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DIALYSIS OF GASTRIC SECRETION IN VIVO WITH A SEMIPERMEABLE DIALYZING BALLOON

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REMOVAL of excess body water and solutes in proper amounts from overhydrated and oversalted patients can be as essential a part of management as correct fluid therapy is to the dehydrated patient. Peripheral, pulmonary, and cerebral edema, ascites, hyponatremia, hyperkalemia, and increase of uremic retention products represent some of the commonly observed body compositional derangements characterized by excesses of body water and its solutes.

In recent years, improved knowledge and development of newer diuretic agents have made it possible to utilize kidney function more effectively to accomplish the objective of water and salt removal. These agents are not uniformly effective, however, and require reasonably good kidney function for their actions. It would seem desirable to be able to remove water and solutes safely without recourse to such measures as peritoneal dialysis, hemodialysis, or intestinal perfusion with the potential difficulties which these methods entail.

Large amounts of water and solutes are secreted into the gastrointestinal tract each day and are rapidly reabsorbed. Studies of gastric heavy water absorption by Cope suggest rapid absorption of water. Evaluation of deuterium oxide secretion into the stomach (8) indicates that gastric juice equilibrates faster with blood than do other areas of body water. Because of rapid reabsorption it is not feasible to harness this daily floodtide very efficiently by continuous aspiration. The possibility, therefore, of introducing into the stomach a semipermeable dialyzing membrane in the form of a balloon was considered. The principle had previously been found effective in the small intestine which was intubated with cellophane tubing (4).

Criteria for the use of a gastric dialyzing balloon were established. It should be easy to introduce through the nose with no more difficulty than the conventional nasogastric tube. The surface should be entirely smooth in order not to provoke gastric bleeding or peptic esophagitis. Nontoxic and nonallergenic, it should withstand prolonged exposure to acid gastric juice without deterioration. As an efficient semipermeable membrane, rapid transfer of water and small solute molecules should occur, but the mem-

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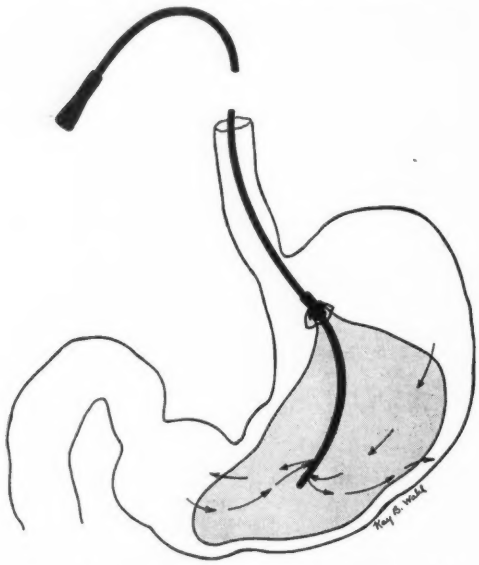

FIG. 1. Semipermeable membrane balloon for dialysis of gastric contents by intermittent infusion and aspiration.

brane must be impermeable to protein, mucus, and cells. Last, it should be easily, quickly, and inexpensively made and therefore should be disposable.

This study was undertaken to devise a semipermeable membrane balloon with these characteristics and to determine water and solute transfers from gastric juice to a dialysate solution contained within the membrane balloon, a procedure termed gastrodialysis (5, 6).

METHOD

Gastrodialysis balloon. About 200 studies were made to evaluate the optimum amounts of collodion, glycerol, ether, and alcohol and the time factors for drying. A technique has evolved for making these membrane balloons in a few minutes.

TABLE I.—PLASMA ELECTROLYTE AND NITROGEN CONCENTRATIONS IN PATIENTS

Patient No.	*Na, mEq./l.*	*K, mEq./l.*	*Cl, mEq./l.*	*BUN mgm. per cent*	*NPN mgm. per cent*
1	143	5.8	111	131	140
2	139	3.4	97	150	179
3	121	5.9	62	162	264

A solution of 6 per cent collodion and 4.2 per cent glycerol in 1:2 ethyl alcohol-ether was evaporated on the inside of a 500 milliliter Kjeldahl flask, the neck of which was cut off to 7 centimeters. After pouring 15 milliliters of the aforementioned solution into the flask, the flask was inverted and drained into a 50 milliliter beaker for 1 minute with the neck of the flask below the surface of the liquid to prevent entrance of air. At the end of this time, the beaker was removed and the inner film was allowed to dry for 5 minutes. The film was extracted intact by running cold tap water between the film and the flask. The balloons were stored in moist gauze in the refrigerator. Prior to use, soft No. 14 polyvinyl tubing was inserted, and the neck of the balloon was tied over a rubber bushing 3 millimeters in diameter with No. 00 cotton. The rubber bushing consisted of a short segment of intact rubber insulation from No. 14 copper wire conduit, as shown in Figure 1.

Tests were made in vitro by filling the balloons with 300 milliliters of saline and immersing them in 1 liter beakers containing 700 milliliters of a solution consisting of potassium chloride, 15 millimoles per liter, and urea, 400 milligrams per cent. Samples of 2 milliliters were taken from the balloon every 15 minutes for 1 hour and were analyzed for potassium and urea nitrogen. The balloon was raised and lowered each 15 minutes to maintain a relatively constant stirring effect. In some additional studies, the effect of agitation was evaluated by stirring the outside bath with a power-driven rotary stirrer.

Additional studies were made with a larger balloon of 600 milliliter capacity. Because of technical difficulties in obtaining a sufficiently thin membrane, transfers were only slightly greater than those across the smaller balloon so that the latter was employed for all subsequent studies.

The thin, flexible, rolled-up membrane balloon with the attached tube was introduced through the nose and was swallowed easily by the human subject. Intubation of

bilaterally nephrectomized dogs was accomplished under anesthesia by sodium pentobarbital, 30 milligrams per kilogram of weight, with the balloon tied on a No. 18 Levin tube.

The balloons and small tubes were swallowed by 3 patients with chronic uremia after the pharynx was sprayed with 5 per cent cocaine. These patients were hospitalized at the University of Kansas Medical Center. Pertinent plasma electrolyte and nitrogen concentrations at the times of gastrodialysis are summarized in Table I.

Patient 1 was a 23 year old male with chronic glomerulonephritis, hypertension, moderate anemia, and azotemia. He was well compensated and relatively symptom-free at the time of study.

Patient 2 was a 19 year old male with chronic glomerulonephritis, anemia (hematocrit 17 per cent), and azotemia. Although he had slowly progressive uremia, he was fairly well compensated, and except for weakness, was symptom-free at the time of study. This patient later had an isolated jejunal segment operation for perfusion and his case has been presented in detail elsewhere (7).

Patient 3 was a 53 year old male with chronic glomerulonephritis with terminal uremia and with oliguria, hypertension, anemia, and azotemia. He had pulmonary edema, bronchopneumonia, and diarrhea with some melena. He was semicomatose and nearly moribund at the time of study. Occasional temporary improvement was associated with adequate tracheal suctioning.

The dialyses were performed by instilling 300 milliliters of the dialysate solution into a funnel or syringe attached to the polyvinyl tube. In various studies, the solution was either aspirated completely at the end of a given time or serial samples were taken and the solution was aspirated at the end of the experimental period. Volumes were measured carefully to define water transfers. The continuous flow system was studied with an outflow pressure of 20 centimeters of water, but experience has been limited with this method. All of the data being reported have been obtained by intermittent infusion and aspiration and by periodic sampling because of the greater technical precision afforded in the measurement of transfer rates. The system is shown in Figure 2.

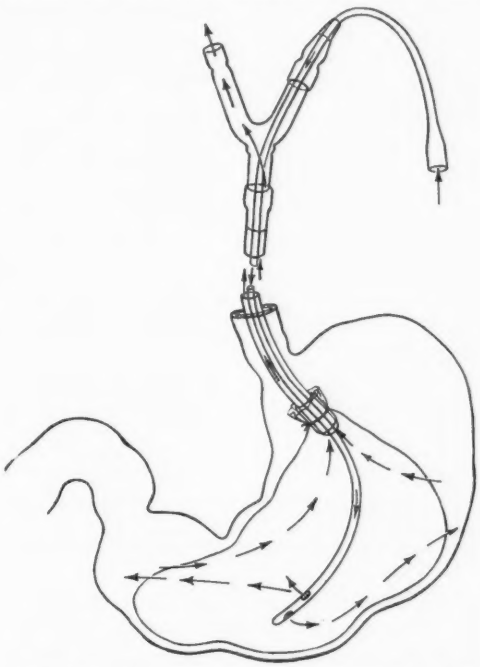

FIG. 2. Semipermeable membrane balloon with double lumen tube for continuous perfusion and dialysis of gastric contents.

The composition of the dialyzing solutions varied as shown in Table II but included no potassium or nitrogen. Either hypertonic glucose or sucrose solutions were used for water removal studies. Water transfers were determined by measurement of dialysate fluid volumes in graduated cylinders and by relating the change of this volume to the volume instilled.

Analyses of the perfusate solution were done by standard methods employing the Beckman DU flame spectrophotometer for sodium and potassium, the Volhard titration for chloride, the dioxime reaction for urea nitrogen, the Kjeldahl nitrogen procedure for nonprotein nitrogen, a modified ethylenediamine tetra-acetic acid titration for calcium and magnesium, and the Beckman Model G *p*H meter for *p*H. In each study a sample of the dialysate solution employed was analyzed for the various electrolytes and crystalloids in the same ways as were

TABLE II.—GASTRODIALYSIS REMOVAL RATES

Patient No.	*Series*	*Dialyses*	*Dialysate*	*H_2O ml./hr.*	*Na mEq./hr.*	*K mEq./hr.*	*Cl mEq./hr.*	*P mgm./hr.*	*NPN mgm./hr.*	*Glucose transfer gm./hr.*
Normal subject										
	A	1(3)	0.9% NaCl			1.7±0.1			26±5	
	B	1(4)	0.9% NaCl-1% Glucose			2.2±0.5				
	C	1(4)	0.9% NaCl-1% Glucose			1.7±0.5				
	D	6	0.9% NaCl			3.2±0.9			39±8	
1										
	A	7	32		1.2±0.6	0.6±0.1		4.2±1.6	33±8	
	B	2	33		1.9±1.0	0.6±0.03		3.6±0.4	41±23	
	C	3	25% D/W	21±11		0.7±0.1			36±7	9.6
	D	2	50% D/W	65±2		0.8±0.1			46±7	
	E	3	50% D/W	76±18	5.8±1.6	1.3±0.2	14±2		117±23	22±8
2										
	A	6	5% D/W	20±12	4.1±2	1.8±0.4	22±3		63±34	6.5±1.4
	B	2	50% D/W	103±37	3.7	1.8±0.8	24		99±45	18.9
	C	2	85% S/W	127±11	3.5	1.5±0.7	19		81±10	
3										
	A	8	30			0.5±0.3			97±62	

Values represent averages followed by standard deviations. Numbers in parentheses refer to the number of samples taken for at least 1 hour. Dialysate 30 contained H^+, 30; Na^+, 50; Ca^{++}, 20; and Cl^-, 100 mEq. per liter of 5 per cent glucose. Dialysate 32 contained Ca^{++}, 18; H^+, 80; and Cl^-, 98 mEq. per liter of water. Dialysate 33 was the same electrolyte composition as 32 in 5 per cent glucose.
Symbols: D/W = dextrose (glucose) in water; S/W = sucrose in water.

the unknown dialysate samples. Concentration times the volume infused was subtracted from the concentration times the volume removed to obtain values for the transfer of each electrolyte and crystalloid. Standard deviations, linear regression equations, and coefficients of correlation were calculated by conventional equations. Each balloon was tested for gross leakage after removal from the stomach either by filling with methylene blue solution and observing for evidence of pinhole leaks into an outside bath or by instilling radioactive iodinated albumin and sampling the outside bath for radioactivity in a gamma well scintillation detector. In all of the studies reported here, no leakage was evident by these methods used for detection.

RESULTS

In vitro. A collodion and glycerin semipermeable membrane balloon was developed which fulfilled the necessary criteria. The globular shape was found necessary to prevent bunching of the material where it was tied around the tube and to prevent roughened surfaces which might abrade the gastric mucosa or aggravate esophagitis. Exposure to acid gastric juice for more than 24 hours did not change the membrane permeability.

Transfers of potassium and urea into the semipermeable membrane balloon at a rate equal to 30 per cent of the outside dialyzing bath concentration in 15 minutes were observed as shown in Figure 3. It was found, in addition, that the membrane was impermeable to radioiodinated albumin and only slowly permeable to methylene blue, with a molecular weight of 320, thereby confirming the semipermeable characteristics of this collodion and glycerol membrane. About 1 out of 5 of the balloons developed pinhole leaks which were probably related either to tiny air bubbles in the collodion and glycerol film or to specks of particulate matter on the inside of the flasks used in preparation of the membranes. All data obtained with such defective membranes have been excluded.

In the normal subject, by using balloons of different capacities it was observed that a volume of less than 600 milliliters was well tolerated and produced no symptoms of fullness. In one earlier study in which the balloon broke while in the stomach, the time at which this occurred was not evident until the analytical results from frequent sampling

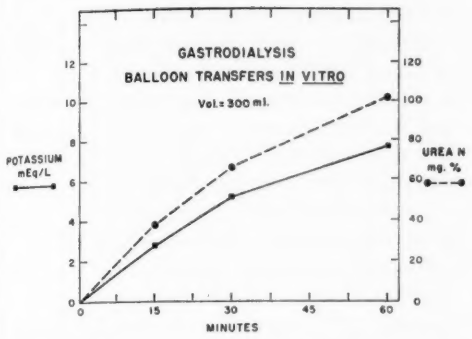

FIG. 3. Dialysis against an outside solution containing 15 millimoles of potassium per liter and urea 400 milligrams per cent (urea nitrogen 187 milligrams per cent). Concentrations within the balloon show an exponential increase and are about half those of the outside solution at 1 hour.

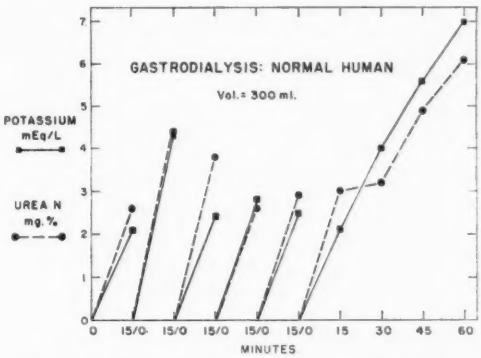

FIG. 4. Successive 15 minute dialyses were followed by a 1 hour dialysis with 15 minute samples in this subject. Similar slopes for each of the dialyses indicate that potassium and nitrogen are made available at the surface of the balloon as rapidly as they are transferred across the membrane.

were available. Precipitious changes in sample concentrations showed that the balloon had ruptured 80 minutes after intubation.

Figure 4 summarizes the results obtained in a study in the normal subject, in which 300 milliliters of solution, containing no potassium or nitrogen, was infused, aspirated, and replenished each 15 minutes for 75 minutes. Fresh solution was again reinstilled and samples were taken each 15 minutes for the next hour. The nearly identical slopes of the 15 minute curves indicate that potassium and nonprotein nitrogen were made available at the surface of the membrane more rapidly than the rate of removal by dialysis. In Table II are summarized the removal rates in the normal human subject. Removal of about 2 milliequivalents of potassium and 25 to 40 milligrams of nonprotein nitrogen per hour were observed in 17 samples. Figure 5 illustrates the transfer of hydrogen ion as calculated from p_H changes using a 450 milliliter volume of dialysate. From the transfers of hydrogen and chloride observed, it is apparent that over 10 millimols of hydrochloric acid crossed the membrane each hour in this subject. In other studies it was found that a neutralizing alkali in higher concentration could transfer out of the balloon as the hydrogen and chloride transferred in, thereby accomplishing neutralization of gastric juice.

The importance of maintaining a high concentration gradient across the membrane is illustrated in Figure 6. Potassium removal was exponentially and inversely related to the time 300 milliliters of dialyzing fluid remained within the balloon in this study on the normal subject.

Evaluation studies in 2 bilaterally nephrectomized dogs under anesthesia with sodium pentobarbital, 30 milligrams per kilogram, showed removal of nitrogen in proportion to the plasma concentration. In one study, with a plasma nonprotein nitrogen concentration of 226 milligrams per cent, nitrogen was removed at a rate of only 33 milligrams per hour while potassium removal was only 0.1 milliequivalent per hour. The unknown influence of anesthesia together with multiple variables introduced by nephrectomy itself made difficult the interpretation of the data and their correlation with the normal human and uremic patients. Although it was hoped in the initial phase of study of these anesthetized dogs that a beneficial effect might be obtained, it soon became apparent from the chemical data that this could not be expected under these conditions. Survival studies therefore were not made.

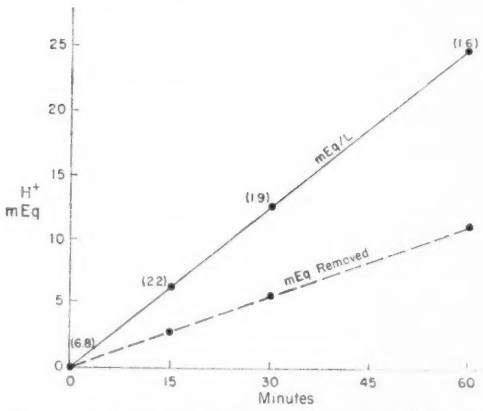

FIG. 5. Removal of hydrogen ion by gastrodialysis is shown. The solid line represents the concentration of hydrogen ion. The numbers in parentheses indicate the *p*H values for each sample. The dashed line portrays the amount of hydrogen ion removed in the dialysate volume of 450 milliliters of 0.85 per cent sodium chloride. About 10 milliequivalents were removed each hour.

Studies in patients. The gastrodialysis balloon was introduced easily into each of the patients after spraying the pharynx with 5 per cent cocaine. Vomiting, regurgitation, or retching did not occur after the balloon was in the stomach.

Patients 1 and 2 were reasonably well compensated with their chronic uremia. The clinical course of patient 1 was unaffected by the few gastrodialyses. Patient 2 had hypertension, the blood pressure being 160/112 millimeters of mercury. During one gastrodialysis with 50 per cent glucose, weakness and faintness developed suggestive of the dumping syndrome and the patient had a blood pressure fall to 132/88 millimeters of mercury. This phenomenon, however, did not develop on two subsequent occasions on different days, with hypertonic dialysates. His clinical course, similarly, was otherwise unaffected. Patient 3 was nearly moribund when gastrodialyses were performed. Although his sensorium cleared temporarily 3 hours after gastrodialysis was begun, variable respiratory factors did not permit adequate interpretation and he expired 2 days later of his disease. Autopsy did not reveal any deleterious effects from the gastric balloon.

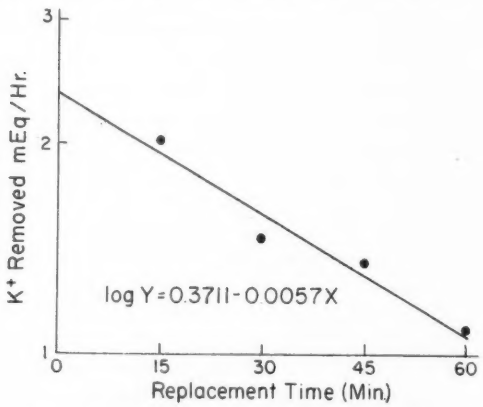

FIG. 6. Semilogarithmic plot of the period the dialysate remained in the balloon and the amount of potassium removed shows the dependence of transfer on concentration gradient.

Observed transfers of water, electrolytes, nitrogen, and glucose are summarized in Table II for the normal subject and the uremic patients. Table I indicates the approximate plasma concentrations at the times the gastrodialyses were done.

The hourly rates of transfer listed in Table II suggest that significant amounts of water, sodium, potassium, chloride, nonprotein nitrogen, and glucose were transferred and that these transfers were proportional to the dialysate compositions. Assuming a 20 hour daily dialysis, 10 to 44 milliequivalents of potassium, 24 to 116 milliequivalents of sodium, 280 to 480 milliequivalents of chloride, 72 to 84 milligrams of inorganic phosphorus, 0.5 to 2.3 grams of nonprotein nitrogen, and up to 2.5 liters of water could be removed each day. Removal of these substances could be reduced or eliminated by increasing their respective concentrations in the dialyzing fluid. Absorption could be produced by increasing their concentrations further. Water removal was directly proportional to the osmolality of the dialysate as shown in Figure 7. Measurement of the *p*H of the dialysate samples afforded an indication of the amount of hydrogen ion removed. The results of one study, employing serial samples, are shown in Figure 5. This

rate would correspond to the removal of about 200 milliequivalents of hydrogen per day. Taken together with the chloride and water values, at least 2 liters of 0.1 normal hydrochloric acid could be removed each day.

Coincident with removal of water and other substances, glucose transferred out of the membrane and became available for absorption by the mucosa. The amount transferred, 130 to 440 grams per day, depended upon the concentration of carbohydrate in the dialysate. The use of 50 per cent glucose would supply as much as 1,800 calories per day.

The dependence of transfers of dialyzable substances upon the concentration gradient across the semipermeable membrane is illustrated for potassium in Figure 6. The exponential nature of the curve suggests this dependence, although linear relationships were frequently observed, as shown for potassium in Figure 4 and for hydrogen in Figure 5. This interesting disparity in vivo can probably be explained by the combination of several factors including concentration gradient, membrane transfer rate, gastric secretory rate, and gastric juice circulation rate between the membrane and the mucosa. Although rapid transfer would be favored by a low concentration within the balloon, maintenance of relatively high concentration at the outside membrane surface would be conditioned by the other factors. The limiting factor, operating at the outside surface of the membrane, is gastric juice mixing and this would be expected to reflect, in linear fashion, steady state availability of any substance presented to it at a constant rate.

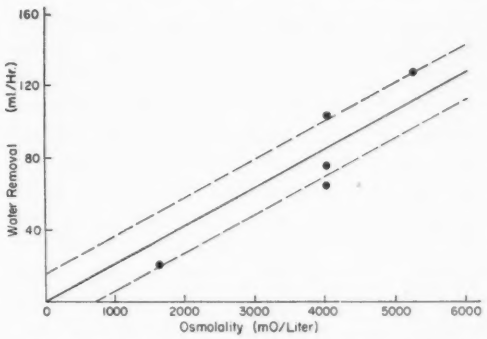

FIG. 7. The proportional relationship between osmolality and water transfer is suggested. The solid line represents the line calculated by linear regression equation and the dashed lines indicate 1 standard deviation (15 ml.) $Y=0.02\ x$; $r=0.92$; $P=0.01$.

DISCUSSION

The transfers of water, electrolytes, and glucose observed suggest the feasibility of removal of predictable amounts of water or electrolyte by this procedure and indicate that caloric needs can be provided at the same time. This experimental study has not included adequate clinical evaluation. This will require an accurate interpretation of the value of gastrodialysis by those individuals concerned with the management of patients with problems characterized by hyperhydremia.

Using our principle of gastrodialysis but with a gastric bag made from sheet cellophane, Marr and associates recently have reported the management of 14 patients with acute renal failure. They employed a constant perfusion and aspiration flow system and devised an ingenious cycling apparatus which provided safeguards in the event of rupture of the membrane and facilitated attention to the procedure. In all of their patients gastrodialysis controlled acidosis while in half of the patients the azotemia was stabilized and the uremic syndrome may have been delayed or prevented. We have not yet used gastrodialysis in acute renal failure, preferring to manage these patients by dietary and fluid and electrolyte measures with fairly liberal indications for hemodialysis if complications supervene. From the data reported here, it is apparent that the potassium removal rates are too slow to warrant the use of gastrodialysis for the treatment of potassium intoxication, in the event that a hemodialyzer is readily available.

One of the limiting factors in transfers into the balloon is the surface area of the

membrane of about 300 square centimeters. By using larger balloons this can be increased, but a threefold increase in volume only doubles the surface area, and technical difficulties in making satisfactory larger balloons have not as yet been resolved. Use of cellophane tubing of 27/32 inch diameter in the small intestine affords sufficient surface area but its introduction has required operative intestinal intubation (4). These studies showed, however, that isotopic water, sodium, and potassium in the blood were transferred into the dialysate.

Studies on the fabrication of semipermeable membranes by many workers have been summarized by Clarke. Newer developments in the study of membrane material and the dynamics of membrane transfers may result in an improved membrane for use for this purpose.

Although no complications were observed in these investigations of the normal human subject or the uremic patients, possible deleterious effects should be listed and sought for in any subsequent studies. Gastric bleeding and esophagitis could occur, although the smooth surface of the diaphanous membrane would tend to obviate the former. Experience with small infant-type polyvinyl feeding tubes for several weeks in patients for tube feeding without development of serious peptic esophagitis would not tend to incriminate this eventuality. Rupture of the balloon could occur and did happen on one occasion without consequence during the second gastrodialysis of the human subject. The reservoir-scale device used by Marr and associates should prevent overadministration of fluid. The membrane balloons, as now made, can withstand several times the pressure which would be employed for gastrodialysis.

The ingenious work of Wangensteen and associates on perfusion of a rubber balloon in the stomach with cold water to inhibit gastric secretion has found practical application by them in the management of patients with bleeding peptic ulcer. The observations in our study suggest the possibility that gastrodialysis would remove hydrochloric acid, and could add neutralizing alkali as well as carbohydrate and amino acids for nutrition. Perfusion of the gastrodialysis balloon with a cold solution would be expected to inhibit gastric secretion, as in the technique of Wangensteen, but decreased membrane transfer and decreased carbohydrate and amino acid absorption would undoubtedly accompany this.

Gastrodialysis has been presented as an investigative procedure which may be of use in the study of several areas of biologic interest. With further development and adequate clinical evaluation, practical usefulness in the management of patients may become apparent.

SUMMARY

1. A semipermeable membrane balloon with attached tube has been developed for insertion into the human stomach to dialyze gastric juice, a procedure termed gastrodialysis.

2. Transfers of water, sodium, potassium, hydrogen, chloride, phosphorus, nonprotein nitrogen, and glucose across this membrane have been determined in the normal human and 3 uremic patients.

3. The rates of transfer have been correlated with concentration gradients and osmolality of the dialysate.

4. By using hypertonic dialysates, over 2 liters of water, 40 milliequivalents of potassium, 100 milliequivalents of sodium, 450 milliequivalents of chloride, 80 milligrams of phosphorus, and 2 grams of nonprotein nitrogen were removable daily in selective combination as determined by the composition of the dialysate.

5. Carbohydrate absorption depended upon the concentration in the balloon and occurred at a maximum rate of 440 grams per day, providing approximately 1,800 calories.

6. This method has been presented as an investigative procedure and its limitations and possible applications have been discussed.

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RENAL AUTOREGULATION

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NUMEROUS REPORTS in the medical literature have shown that there is very little change in the magnitude of renal blood flow when the renal arterial pressure is varied within a range of from approximately 80 to about 190 millimeters of mercury. This so-called autoregulation of renal blood flow is generally viewed as an intrinsic and exclusive property of the kidney. It has been found to be present in the isolated perfused kidney, in the kidney perfused in situ, and when the arterial pressure is altered locally by gradually occluding the aorta above the renal arteries. The present study was carried out in an effort to learn more about this interesting phenomenon.

METHODS

Mongrel dogs ranging in weight from 10 to 26 kilograms and averaging 16.4 kilograms were used. The method employed for measuring directly the renal blood flow has been described in detail previously (3). Changes in the pressure in the distal aorta and the renal arteries were effected by means of a screw-down type of Blalock artery clamp placed across the aorta proximal to the point of origin of the renal arteries (3). Esophageal temperature was recorded throughout each experiment by means of a telethermometer. The temperatures remained normal. Arterial blood pressure was measured by a U-tube mercury manometer introduced through the femoral artery into the aorta below the origin of the renal arteries. In a series of dogs, hemorrhagic hypovolemia was brought about by rapid withdrawal of 20, 30, or 40 cubic centimeters of blood per kilogram of body weight through a catheter introduced into the femoral artery. In one group of animals bilateral thoracolumbar sympathectomy (the fourth dorsal to the fourth lumbar) and splanchnicectomy were performed in two stages. These procedures were carried out about 10 days apart, and the renal flow experiments were made approximately a week after the second operation. In another group of dogs, autoregulation was studied immediately after bilateral section of the vagosympathetic chain in the neck.

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RESULTS

Controls. In Table I and Figure 1 are given the renal blood flows in a control group of 5 dogs in which the renal artery pressure was lowered every 10 minutes by progressive aortic clamping. As the pressure was reduced from 130 to 70 millimeters of mercury, only a slight gradual fall in renal blood flow was noted. At 70 millimeters of mercury, the mean renal blood flow was still 79.1 per cent of the control value. Below the pressure of 70, however, the flow decreased more sharply and at 20 millimeters of mercury, it was only 19 per cent of the control.

Dextrose infusion. In 15 dogs renal blood flow was studied in the same manner except that the animals were receiving throughout the experiment an intravenous infusion of 5 per cent dextrose at an almost constant rate of 0.7 cubic centimeter per kilogram per minute. The average initial renal blood flow was slightly higher—28.1 cubic centimeters

TABLE I.—RENAL BLOOD FLOW IN CUBIC CENTIMETERS PER KILOGRAM OF BODY WEIGHT PER MINUTE AS RELATED TO RENAL ARTERIAL PRESSURE

Wt. of dog, kgm.	*Control observations*	*Pressure induced by aortic clamping*											
		130	*120*	*110*	*100*	*90*	*80*	*70*	*60*	*50*	*40*	*30*	*20*
		CONTROL OBSERVATIONS											
21	24.7	24.8	25	25	23.5	19.4	19.2	17.4	15.1	13.6	10.9	7.3	4.5
15	25	25	23.4	25.5	23.5	25	22.9	22.2	18.1	15.3	12.4	6.4	4.5
20	20.4	19.2	18.9	18.9	18.8	18.9	18	16.6	14.8	10.3	9	7.1	3.4
18	18.5	19	18.8	18.8	17.5	17.3	16.6	15.1	14.1	9.7	8.7	8.3	4.8
23	18		18.4	18	16.6	14.4	14.4	14.6	10	10.8	5.2	6	3.3
Mean	21.6		20.9	21.2	19.9	19	18.2	17.1	14.4	11.9	9.2	7	4.1
		AFTER INFUSION OF 5 PER CENT DEXTROSE											
15.8	26.5				25.2	24.6	24	22.5	22	20.7	17.2	16.3	11.4
14.7	28		26.6	22.6	26	24	22.4	19.6	20.8	19.2	18.3	13	
17	31.2		31.2	28.5	27.2	27.2	23	20	20.8	17.6	16.6		
18	28.5			28.5		26.3	27	22.3	22.3	16.6	15.6		
16.6	28.6	28.6	26.5	25.5	25.5	23.2	22	21.3	20.4	17.5	15.1		
13.8	27.9	26	23	23	23	22.4	22.4	20.6	20.6	17.2	17.2	16.5	12.3
15	27.2			27.2	27.1	24.5	22.6	20.8	20.8	17.6	15.6	19	
14	28.2		28.2	29	24	22.5	20	16.5	16.9	15.2	14	12	
18.8	28.8		28	28	25.3	24.5	18.3	17.8	18	13.6			
20	28		27	24	22	23	24.5	21	20.8	18.9	14.3	9.1	
16.4	32.4		32.4	30	27.7	28	28	26	24	20.8	17.1	14.3	5.6
15.5	31.7			31	27	26	26	24.6	24.6	20	11.7	17.1	11
14.7	30.8			29.6	29.6	27.2	27.2	23.6	23.6	17.2	16.5	11.7	6.4
14.9	26			25	23.2		22.4	21.7	21.1	14.8	13.6	16	7
17	31	27.4	27.4	25.6	25.9	24.5	19.3	19.3	19.3			10	8
Mean	28.1			27.2	25.6	24.8	23.2	21.1	21.2	17.6	15.6	14.1	8.8
		AFTER BILATERAL VAGOTOMY											
14	21.4	21	21.4	21	21.8	20	20	17.8	16.4	14.4	10.7	10	3.8
16	18.7			19.1	18.3	18.2	17.6	16.6	15.6	8.5	8	6	4
10	25	24	23.9	23	23.9	24	24	22.3	20.5	15.3	14	10	1
13	21.3	21.3	22	22	21.6	21	19.8	19	17.6	16	10.5	8	6
20	26.4	26	26	26.4	26	25	20	17	16.3	13.1	10.5	5	3
16	17		16.6	16	16	15.6	11.3	10.8	8.6	7.4	5.3	3.5	0.8
Mean	22.7		21.4	21.2	21.2	20.6	18.7	17.2	15.8	12.4	9.8	7	3.1
		AFTER RENAL DENERVATION											
14	44.5					43.6	43.6	43.6	43.1	37.2	36.5	29.4	6.3
11	30.2					30.2	28.2	28.2	30.2	24.7	24.7	18.9	10.4
12	22.6				22.6	23	22.6	22.2	20	18.9	14.5	11	8
11.4	29.2				30	27.9	30.2	30	30	27.8	24.8	19	10.2
12.8	22.6					22.6	22	18.5	16.6	13.3	13	10.6	5
Mean	29.9					29.4	29.3	28.5	27.9	24.3	22.7	17.7	8
		IN HYPOVOLEMIA											
26	8					6.7	7	6.3	6.4	5.1	4	3.3	1
20.8	4				3.4	3.7	3.9	2.7	2.8	2.2	2	2	2
20.5	5.1		4.2	4.3	4.6	4.1	3.8	3.4	2.2	2.1	1.8	1.7	1.2
16	10.6			11.6	11.4	11.6	11.5	11.5	10.8	9	8	6.7	2.7
13	6.8				7	6.8	6.7	6.4	6	5	5.4	4	3.5
Mean	6.3		6		6.6	6.5	6.5	6	5.6	4.6	4.2	3.5	2

per kilogram per minute—than in the control experiments (2). Only a moderate fall in renal blood flow was noted between the initial pressure and 60 millimeters of mercury. At this level the mean flow was 75 per cent of control. The relation between flow and pressure was essentially the same as that in the preceding group.

Bilateral vagotomy. In 6 dogs autoregulation was studied after bilateral section of the vagosympathetic chains in the neck. No significant difference from the control group was noted. At a pressure of 70 millimeters of mercury, the mean renal blood flow was 75.7 per cent of the control value and at 20 millimeters of mercury it was 13.7 per cent.

Bilateral thoracolumbar sympathectomy and splanchnicectomy. In 5 animals autoregulation was studied 7 to 10 days after complete sympathetic denervation of both kidneys. The renal blood flow in this group was significantly higher than in the control group. At distal aortic pressures of 100 and 90 millimeters of mercury it was 50 and 55 per cent

FIG. 1. Chart showing autoregulation in normal controls, *C*, animals previously subjected to sympathectomy and splanchnicectomy, *S*, those receiving an infusion of 5 per cent dextrose, *D*, those with section of the vagosympathetic trunks in the neck, *V*, those rendered hypovolemic by bleeding 20, 30, or 40 cubic centimeters of blood per kilogram, H^1, and those made hypovolemic by bleeding 20 cubic centimeters per kilogram and subjected to aortic clamping in order to reduce the aortic pressure at the renal level, H^2.

above the control values. The augmentary effect of sympathectomy upon renal blood flow was even more evident in the lower pressure range. For instance, at distal aortic pressures of 40 and 30 millimeters of mercury, the mean renal blood flow in the sympathectomized group was 247 and 253 per cent above the corresponding values in the control animals at the same pressures. In spite of the relatively large renal blood flow in the sympathectomized group, the pattern of autoregulation was still evident. No significant change in renal blood flow was observed at arterial pressures of 110 and 60 millimeters of mercury. A progressive fall in renal blood flow was observed as pressures were reduced below 60 millimeters of mercury.

Hypovolemia. In 64 dogs renal blood flow was measured after acute withdrawal of 20, 30, and 40 cubic centimeters of blood per kilogram of body weight. The femoral pressures in these hypovolemic animals ranged from 155 to 5 millimeters of mercury. The data are shown in Figure 1, H^1. Here are summarized the average renal blood flows observed at various systemic blood pressures. A total of 499 determinations were made. Each dog was studied every 5 minutes for a period of 30 minutes after hemorrhage. The systemic blood pressure fell initially and gradually tended to be restored in the group bled 20 cubic centimeters per kilogram of body weight. It tended to remain low or to decrease further in the animals in which a more severe hemorrhagic shock was induced. The curve H^1 in Figure 1 was constructed by recording all these random data and plotting together the values of renal blood flows at various blood pressure levels. Wide variations in value were observed, but in general the average renal flows were about the same between systemic pressures of 155 and 90 millimeters of mercury. Below a pressure of 90 a gradual slight decrease in flow was observed. The characteristic pattern of renal autoregulation was clearly evident, although the values of renal blood flow were much lower as a consequence of hemorrhage. Indeed, the effect of autoregulation seemed to extend even into the lower pressure ranges. In the majority of the animals studied the measured renal blood flow was less than 7 cubic centimeters per kilogram per minute (Fig. 2). From 21 to 48 per cent of the 234 renal blood flow measurements in those hypovolemic animals with blood pressures ranging from 105 to 155 millimeters of mercury fell below this level.

In 5 dogs bled 20 cubic centimeters per kilogram, renal flows were studied during a 30 minute control period. The distal aortic pressure was then gradually lowered by decrements of 10 millimeters of mercury by means of suprarenal aortic clamping, and renal flows were measured at each level of pressure. Further evidence that autoregulation is present in hypovolemic animals was observed (Fig. 1, H^2). Almost no change in renal flow was noted when the distal aortic pressure was decreased from the original posthemorrhage value to about 60 millimeters of mercury and, indeed, there was little change as the pressure was further reduced.

DISCUSSION

The literature pertaining to autoregulation of renal blood flow has been reviewed elsewhere (1, 3). The studies recorded in the literature are principally concerned either with normovolemic animals in which the kidneys were perfused in situ or with perfusion of isolated kidneys. In our experiments the kidneys were not disturbed, in order to avoid possible alteration of renal circulation as the consequence of direct trauma. In all of the groups studied, autoregulation of renal blood flow was observed. The renal flow dropped significantly only when the distal aortic or the systemic pressure was below a critical value of from 80 to 60 millimeters of mercury, regardless of whether the circulating blood volume was normal or reduced. We were interested in the possible role of the neurovegetative system in the phenomenon of autoregulation. The work of Henry and Pearce, suggesting the existence of stretch receptors in the left atrium which, when properly stimulated, would cause diuresis, made us wonder whether the rise of pressure in the proximal aorta and left side of the heart provoked by the gradual occlusion of the suprarenal aorta would stimulate such receptors and enhance renal flow. There was no evidence that this occurred. Since section of the vagus nerves in the neck is usually regarded as adequate inactivation of the buffer nerves, autoregulation was studied in a group of vagotomized dogs. There was persistence of autoregulation under these conditions. We also studied the phenomenon in animals with sympathetically denervated kidneys. In these animals renal blood flow was also maintained at about the original value until a renal arterial pressure of about 60 millimeters of mercury was reached. Despite the augmentation of basic renal flow in the sympathectomized animals and in those receiving an infusion of dextrose, the phenomenon of autoregulation was present. Similarly it was observed in animals in which the basic renal blood flow was reduced by hemorrhage.

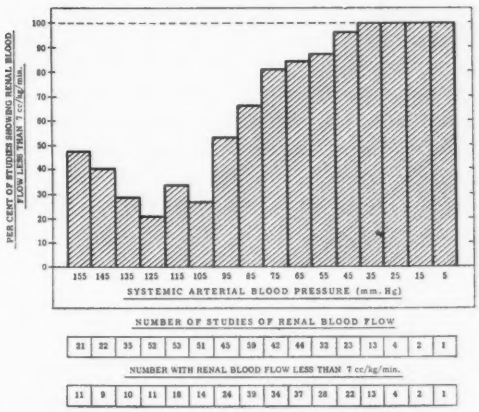
PER CENT OF STUDIES SHOWING RENAL BLOOD FLOW LESS THAN 7 CC/KG/MIN.
100
90
80
70
60
50
40
30
20
10
0
155 145 135 125 115 105 95 85 75 65 55 45 35 25 15 5
SYSTEMIC ARTERIAL BLOOD PRESSURE (mm. Hg)
NUMBER OF STUDIES OF RENAL BLOOD FLOW
21 22 35 52 53 51 45 59 42 44 32 23 13 4 2 1
NUMBER WITH RENAL BLOOD FLOW LESS THAN 7 cc/kg/min.
11 9 10 11 18 14 24 39 34 37 28 22 13 4 2 1

FIG. 2. Chart showing renal blood flow at various levels of arterial blood pressure in animals rendered hypovolemic by hemorrhage. Below each blood pressure level are recorded the total number of studies, from which the mean values of renal flow were calculated, and the number with flows of less than 7 cubic centimeters per kilogram per minute.

Clinicians have commonly assumed that even in the hypovolemic state a normal or near normal blood pressure gave assurance of adequate renal blood flow. Many have believed that one need not be concerned about renal flow when the systemic pressure is 80 millimeters of mercury or greater. Our studies demonstrate that such assumption is erroneous, at least in the dog. Previous studies from this laboratory have demonstrated that a renal blood flow of approximately 7 cubic centimeters per kilogram of body weight per minute is necessary for 100 per cent survival of animals subjected to measured renal autoperfusion over a 2½ hour period. Analysis of 499 direct measurements of renal blood flow in hypovolemic animals demonstrates that renal blood flow was below this critical level in two thirds of the measurements made at a systemic pressure of 85 millimeters of mercury. The same finding was obtained in over half of those measurements made at a systemic pressure of 95 millimeters of mercury and in from 21 to 48 per cent of those carried out in animals with pressures ranging from 105 to 155. Should the same response characterize man,

one could not rely upon normal or near normal pressures in the hypovolemic state as assurance of adequate renal blood flow. In subsequent experiments (1) in which autoregulation was studied by in situ perfusion studies, autoregulation was also shown to be present in normal dogs as well as in vagotomized and renally denervated animals.

SUMMARY

The phenomenon of relative renal autoregulation in normovolemic dogs is confirmed. Autoregulation is demonstrated in normovolemic dogs in which the basic renal blood flow is increased by an infusion of dextrose. Neither vagotomy nor sympathectomy abolishes renal autoregulation. It is present in animals rendered hypovolemic by acute hemorrhage. Renal blood flow is demonstrated to be generally reduced, often to critically low levels, in hypovolemic animals even when the arterial blood pressure is at normal or near normal levels.

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SKIN HOMOGRAFT REJECTION IN ADRENALECTOMIZED AND GONADECTOMIZED INDIVIDUALS MAINTAINED ON METICORTEN

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THIS STUDY was undertaken to investigate the action of maintenance doses of meticorten on the immune response of adrenalectomized and gonadectomized patients to homotransplanted skin, and to note the effects of the administered steroid on the survival of their skin when transplanted to normal subjects.

The similarity of mammalian reactivity to certain foreign proteins and to homografts of various tissues and organs has led to the inference that skin homograft rejection is an immune type reaction. The antigenicity of cytoplasmic and nuclear protein complexes is postulated by Gorer as being the excitor of this reaction. Although no serum antibodies have as yet been demonstrated consistently against these antigens in man, homograft rejection in other respects satisfies the criteria of an immune reaction. Gibson and Medawar have shown that skin homografts in man require a latent period for the development of host reactivity and demonstrate the phenomenon of an anamnestic reaction when they are reapplied after immunity has been established.

Billingham, Krohn, and Medawar (2) noted that in rabbits skin homograft rejection was significantly delayed after the administration of unphysiologic doses of cortisone. Dews and Code demonstrated that in intact or adrenalectomized rabbits, treated with cortisone, circulating antibodies were reduced in response to daily antigen injections. Long, Katzin, and Fry related this effect on antibody production in part to impaired synthesis initiated by the negative nitrogen balance fostered by the hormone. That the effect of cortisone on the immune reaction was not entirely dependent on a negative nitrogen balance was implied by Billingham and his coworkers (3) who delayed skin homograft rejection by treating the graft bed and the skin homograft with cortisone. Skin homografts applied to other areas of the same experimental animal were rejected in the usual time sequence, indicating that the locally applied cortisone had little, if any, effect on systemic immunity.

During wound healing, cortisone, when administered to experimental animals, has been shown to inhibit fibroblastic differentiation and growth and to impede capillary tuft and fibrin formation. Since a skin homograft take is dependent upon its initial fibrinous adhesion to the graft bed and to host vascular perfusion and penetration, cortisone may initially act by delaying graft fixation and vascularization. Subsequently, by limiting the blood supply to the grafts and contact by the formed cellular elements in the blood believed to mediate graft destruction, cortisone might forestall or alter the nature of the ultimate rejection phenomenon.

MATERIAL AND METHOD

One hospitalized and 3 gainfully employed, asymptomatic, bilaterally adrenalectomized and gonadectomized patients

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TABLE I.—SKIN HOMOGRAFT REJECTION

Recipients	*Rejection time, days*	*No. of cases*
Normal males		
Volunteer homografts	12 to 15	4
Adrenal homografts	9 to 11	4
Adrenalectomized patients		
Volunteer grafts	11 to 20	3
Adrenal grafts	10 to 18	3

maintained on 50 to 70 milligrams of meticorten in divided daily doses for periods of from 1 to 3 months prior to homografting, with advanced hormone dependent neoplastic disease, and 4 Caucasian male volunteers were chosen for this study. Two of the adrenalectomized patients were white females who, prior to adrenal surgery had undergone bilateral oophorectomies, and 2 were males, 1 Caucasian and 1 Negro, who had had previous bilateral orchiectomies. The range in age of these patients was from 46 to 66 years.

Cases 1 through 4 summarize the salient details of the clinical histories:

CASE 1. A 53 year old male Negro underwent a left radical mastectomy in July 1952 at Presbyterian Hospital, New York, for an undifferentiated carcinoma of the left breast. Three and one-half years postoperatively, pulmonary metastases and lymphedema of the left upper extremity were noted. In February 1956, he was admitted to Francis Delafield Hospital and a bilateral orchiectomy was performed, with achievement of partial resolution of the pulmonary metastases. Ten months postoperatively, additional metastases developed in the left and right sides of the supraclavicular area which necessitated a left and right adrenalectomy respectively, in February and March of 1957. Postoperatively, the patient was gainfully employed up to the time of his elective admission in September 1957 for skin homografts. After this procedure, he returned to work and did well until his death in February 1958, following an episode of acute adrenal insufficiency associated with widespread generalized neoplastic metastases.

CASE 2. A 66 year old white male was admitted to Francis Delafield Hospital in May 1955 with an expanding mass of 5 years' duration in the right axilla associated with a mass of 8 months' duration in the supraclavicular area on the right. In June 1955, a biopsy of the right axillary mass revealed an undifferentiated carcinoma of a supernumerary mammary gland. A bilateral orchiectomy was then performed and stilbestrol therapy instituted without apparent effect. In April 1956, a bilateral adrenalectomy was performed with resultant regression of the neoplastic disease. Radiation therapy given additively brought about still further regression, permitting the patient gainful employment. In September 1957, he was electively admitted for skin homografts. After discharge he was followed up in the clinic until his final admission in January 1958 for a cerebral vascular accident. Death occurred in February 1958.

CASE 3. A 46 year old white female was admitted to Francis Delafield Hospital in June 1956 with bilateral breast carcinoma, in association with osteoblastic and osteolytic metastases. In July 1956, a bilateral oophorectomy and a right adrenalectomy were performed, and in August 1956 a left adrenalectomy was carried out. This patient was gainfully employed and asymptomatic up to the time of admission in September 1957 for elective skin homografts. After discharge from the hospital she was readmitted on 3 separate occasions before her death at home in April 1958.

CASE 4. A 58 year old white female had a left radical mastectomy for carcinoma of the breast in January 1956. In July 1957, she was admitted to Francis Delafield Hospital with generalized osseous and visceral metastases. In August 1957, she underwent a bilateral oophorectomy and adrenalectomy, after which she improved symptomatically. In September 1957, 1 month after the last surgical procedure, elective skin homografts were applied. The patient remained hospitalized except for a 1 month interval, until her death in April 1958.

The volunteers were chosen from among the male urologic patients at the Francis Delafield Hospital and ranged in age from 45 to 64 years. All had uncomplicated prostatic hypertrophy and had been admitted for prostatic biopsy.

Baseline eosinophil counts, using Swanson's modification of Randolf's technique, and filter paper electrophoretic serum protein studies, employing Osserman's method, were obtained on all patients. Under local 1 per cent procaine anesthesia, 4 segments of skin measuring 2 by 3 centimeters and approximately ten-thousandths of an inch in thickness were removed from each patient. The wounds were disposed at least 10 centimeters apart, 1 in each of the 4 abdominal quadrants (Fig. 1). After removal of the skin, 3 of the denuded areas were excised down to the subcutaneous fat and the dermis was discarded, bleeding vessels were clamped and tied with No. 5-0 plain catgut. On 3 of these defects, in each

of the 8 patients, a skin autograft, a skin homograft from an adrenalectomized individual, and a homograft from a normal male volunteer were secured in place with interrupted sutures of No. 5-0 dermalon after India ink had been tattooed into the Caucasian homografts with a No. 18 hypodermic needle for purposes of identification (Fig. 2). The remaining defect, with dermis intact, was left denuded in 2 adrenalectomized patients and in 2 normal volunteers, and the dermis was removed in the other 4 subjects. Xeroform gauze and a dry sterile pressure dressing were applied over all operative areas. Postoperatively, all wounds and grafts were inspected each day and redressed with xeroform gauze. Sutures from the grafts were removed on the seventh postoperative day.

Healing of the open wounds was checked by inspection and biopsy. Autograft vascularization was evaluated by observing changes in the color of the graft after transplantation. The degree of contracture of the grafts was recorded by measuring the surface area of each graft once a week.

After primary take had occurred, the homografts were observed for the earliest evidence of rejection by noting changes in their external characteristics. This rejection was most frequently manifested by the formation of sporadic areas of hemorrhage beneath the surface epithelium. Occasionally, in other sections of the surface of the homografts, color changes from pink to blue, pale gray, or white occurred. Areas of dry gangrene followed when rejection did not result in epithelial denudation and serum exudation. After rejection had commenced, the host skin surrounding the grafts usually became and remained inflamed until the graft bed was healed by secondary intention. Throughout the experiment, random punch biopsies were taken of both autografts and homografts to evaluate the differences in elicited vascular and cellular response between control and adrenalectomized patients. Serial eosinophil counts were taken between 8 and 10 p.m.

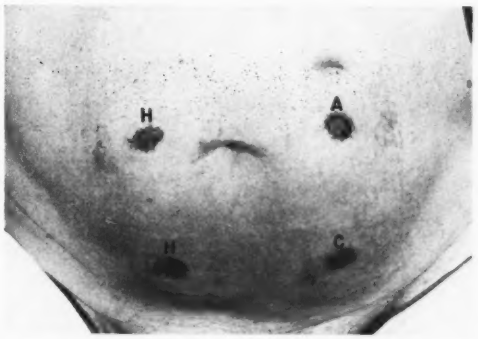

FIG. 1. The disposition of autografts and homografts in the patients studied. The homografts (*H*) are placed to the right of the midline and the autograft (*A*) directly to the left of the umbilicus. A partially de-epithelialized control wound is located in the left upper abdominal quadrant (*C*).

daily, and fasting serum protein electrophoretic studies were made in order to follow the possible systemic effects of homograft rejection. The control wound sites were inspected and punch biopsy specimens taken.

RESULTS

Autografts in both groups of patients exhibited primary take ranging between 90 and 100 per cent in all instances. They were well vascularized by the third or fourth day after grafting and were firmly attached to their beds by the sixth day. Contracture of all grafts occurred maximally during the first month, persisting to the third month, and amounting to not less than 30 per cent nor more than 45 per cent of the original surface area of the grafts. No dissimilarity in graft contracture of adrenalectomized patients and controls was apparent.

Homografts demonstrated primary take with a survival range of 90 to 100 per cent and were indistinguishable from autografts by inspection and biopsy until the first evidence of rejection was apparent (Table I). Inasmuch as biopsies of the homografts demonstrated an asynchronous rejection of epithelium throughout the graft with occasional persistence of epithelial viability for periods in excess of 5 days following the initial appearance of rejection, the time re-

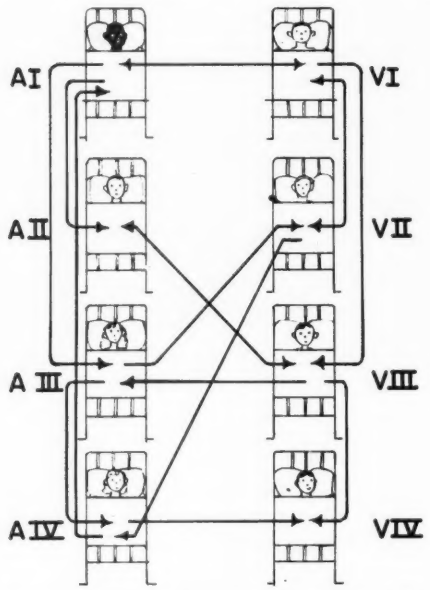

FIG. 2. Schema of cross homografting in subjects studied. Each patient received a homograft from a male volunteer and from an adrenalectomized individual. *A*, adrenalectomized and *V*, volunteer.

quired by the host for the homograft bed to heal was selected as a relative end point of rejection (Table II). Although the latter criterion is subject to error, particularly in instances in which the entire homograft is rejected several days after the onset of manifest tissue incompatibility, and in cases in which homograft dermis is overgrown by epithelium from the host, in no instance in this experiment was there noted such a vigorous rejection phenomenon nor was it possible to show conclusively by sex chromosomal studies that homograft dermis had survived after host epithelial overgrowth.

With the notable exception of 1 hospitalized female adrenalectomized patient (Case 4), homograft rejection in adrenalectomized individuals maintained on meticorten followed the same pattern as the controls. Asynchronous rejection of dual homografts transplanted to the same host did not suggest causality in this small group of patients (Table III). Biopsies revealed no differences in the degree or kind of cellular or vascular reaction which accompanied rejection of homografts in either group of patients and corresponded with observations made by Gibson and Medawar. Secondary healing of the grafted sites after homograft rejection progressed without inhibition in both adrenalectomized and in normal patients.

TABLE II.—SECONDARY HEALING AFTER HOMOGRAFT REJECTION

Recipients	*Healing time, days*	*No. of cases*
Normal males		
Volunteer homografts..	22 to 27	4
Adrenal homografts....	20 to 23	4
Adrenalectomized patients		
Volunteer homografts..	22 to 30	3
Adrenal grafts.....	20 to 25	3

The homografts of the female adrenalectomized patient who demonstrated no external signs of rejection appeared moderately altered from their original state after a period of 6 months. The surfaces of the grafts had become glazed, their borders less distinct, the India ink markings less vivid and more diffuse, their color bluish-gray, and their size decreased by almost 30 per cent. Two biopsies performed at 2 month intervals during the 6 month period showed minimal cellular reaction in the corium and subcutaneous tissues, with gradual obliteration of rete pegs. In 1 homograft transferred from a male donor, it was possible to show complete replacement of epithelium and dermis by the host through reference to the nuclear sex chromosomal pattern of biopsy specimens (Figs. 3 and 4). In the remaining homograft transplanted from a female, one could infer that it too had been replaced by noting the dispersal of its original India ink markings into the deep subcutaneous blood vessel endothelium of the host (Fig. 5). In association with the migration of the colloidal particles, the surface epithelium was noted to be devoid of its papillary intradermal projections. The autograft in this patient maintained its corrugated epithelial surface, its vivid tatoo, its elasticity, and its rete pegs emphasizing the importance of utilizing control grafts to monitor homograft survival.

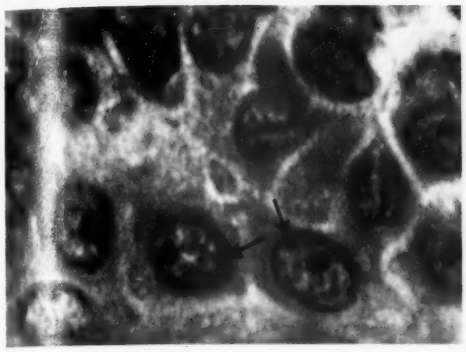

FIG. 3. Photomicrograph of epidermis of skin graft to adrenalectomized patient. Note the chromatin pattern of the epidermal cell nuclei. ×925.

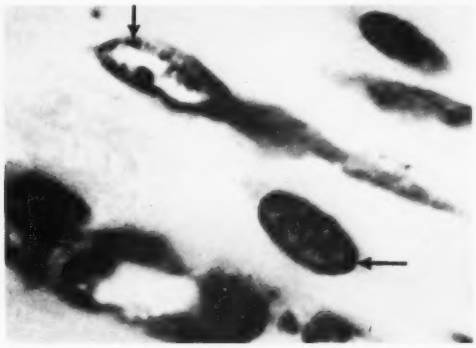

FIG. 4. Photomicrograph of dermal stroma just beneath epidermis of skin graft to an adrenalectomized patient. Note chromatin pattern of fibrocytes. ×925.

Serial serum electrophoretic protein patterns in adrenalectomized patients yielded no changes from those observed preoperatively (Fig. 6). The moderate decrease in gamma globulin noted in 3 patients did not alter the time sequence of homograft rejection in 2 but may have contributed to the nature of the rejection in the 1 remaining instance (Case 4). Electrophoretic patterns of controls were normal before the grafts were applied and did not change during the process of homograft rejection.

Eosinophil response to homograft rejection followed no definite pattern in the 8 patients in this investigation. Preoperative eosinophil values ranged from 50 to 99 cells per cubic millimeter in the adrenalectomized patients, and 85 to 200 cells per cubic millimeter in the volunteers. In no case did the count exceed 300 cells per cubic millimeter before or during the period of homograft rejection. Whenever the count did rise above the preoperative baseline value, it was never sustained for longer than 24 hours.

Healing of open wounds on adrenalectomized patients and controls demonstrated no divergence from accepted norms. They were carefully compared both by observation and biopsies taken at 7, 14, and 21 days from the wound margins. Epithelization over the dermis ranged from 7 to 10 days, and over the subcutaneous fat from 21 to 30 days. Granulation tissue which formed over subcutaneous fat was not deficient, nor was capillary tuft formation or cellular infiltration abnormal. No irregularity in wound healing was observed in Case 4 in which the control site was excised to subcutaneous fat and the homograft was found to be replaced insidiously.

DISCUSSION

The failure to demonstrate significant differences in survival time of homografts transplanted from normal volunteers to 3 of 4 adrenalectomized patients maintained on meticorten suggests that the immunologic mechanisms of these adrenalectomized patients maintained on meticorten were not adversely affected by the administered steroid. The fact that meticorten replacement

TABLE III.—ASYNCHRONOUS REJECTION OF DUAL HOMOGRAFTS

	*Onset donor homograft rejection**		*Secondary healing of recipient graft bed**	
Recipients	*Adrenalectomized homograft*	*Volunteer homograft*	*Adrenalectomized homograft bed*	*Volunteer homograft bed*
AI	AII 10	VI 11	AII 20	VI 23
AII	AI 14	VIII 9	AI 25	VIII 20
AIII	AI 18	VIII 10	AI 24	VIII 23
AIV	AIII G. R.	VII G. R.	AIII —	VII —
VI	AI 20	VII 12	AI 30	VII 22
VII	AIII 12	VI 15	AIII 25	VI 27
VIII	AII 12	VI 13	AII 22	VI 23
VIV	AIV 11	VIII 14	AIV 26	VIII 25

*In days postgrafting.
A, adrenalectomized patient.
V, volunteer patient.
G. R., gradual rejection.

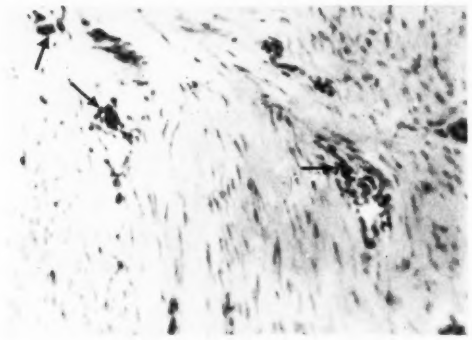

FIG. 5. Photomicrograph showing localization of India ink (arrows) particles used to tattoo Caucasian homografts in the blood vessel endothelium of the subcutaneous tissue. ×109.

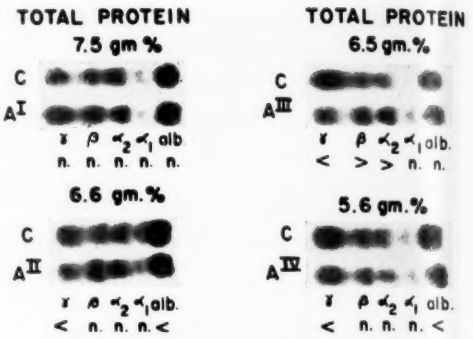

FIG. 6. Preoperative serum protein filter paper electrophoretic patterns in adrenalectomized patients. Note that the gamma globulin values were decreased (<) in 3 patients. *C*, control; *A*, adrenalectomized patients.

in adrenalectomized patients did not affect the survival time of the skin when transplanted implies that this steroid in the dosage employed in the patients studied did not alter the antigenic state of the homograft nor did it affect by absorption from the transplanted skin the immune reactions of the host. Asynchronous rejection of homografts transplanted to the same recipient implies the existence of antigenic disparity between skin homografts and either hypoactivity or hyperactivity on the part of the recipient to dissimilar skin antigens. The lack of significant change in protein electrophoretic fractions and, particularly, in gamma globulin correlates with the failure of Allgower, Blocker, and Engley to identify serum antibodies to homografts. However, despite the existence of a normal serum protein electrophoretic pattern, significant alterations in isohemagglutinin titers following skin homograft rejection, as well as the development of unidentifiable hemagglutinin antibodies, have been demonstrated in man (7). Our inability to elicit eosinophilia during homograft rejection similar to that recorded by Rogers, Converse, Taylor, and Campbell might be due to the failure of the homografts employed in this experiment to supply by virtue of their small size, an adequate stimulus for such a response.

Absence of the external changes indicating homograft rejection in 1 adrenalectomized patient and the demonstration that replacement of homografted skin had taken place indicates the need for caution in determining homograft survival by reference to the outward changes in the homograft alone. The indolent nature of the rejection in this patient was probably related to an inadequate immunologic response to the antigens of the homograft fostered by the pre-existence of hypoproteinemia and marked hypogammaglobulinemia (Fig. 6, Case 4). The ancillary role of neoplasia and meticorten therapy is difficult to evaluate. Neoplasia has not been demonstrated to consistently affect the immune reaction to certain antigenic substances, nor has the malnutrition which it causes. Properdin, which figures significantly in immunity, has been demonstrated to be reduced in about one-half of one group of cancer patients studied by Rottino, Levy, Conter, and Ehnes.

CONCLUSIONS

1. Survival time of homografts transplanted to adrenalectomized patients maintained on meticorten did not significantly differ from controls in 3 out of 4 adrenalectomized patients.

2. Meticorten maintenance therapy in adrenalectomized patients failed to influ-

ence the survival of their skin when transplanted.

3. No significant changes were observed in eosinophils or in serum protein electrophoretic patterns of both control and adrenalectomized patients either during or after homograft rejection.

4. It was demonstrated that homograft rejection occurred insidiously in 1 adrenalectomized patient without the occurrence of overt epithelial denudation.

5. Wound healing as evaluated in this investigation in adrenalectomized patients maintained on meticorten did not differ from the controls.

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CARCINOMA IN CHRONIC THYROIDITIS

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RENEWED INTEREST in the subject of chronic thyroiditis has been aroused by the work of Witebsky and his associates in Buffalo, that of Roitt and associates, of Thompson, and of White in Great Britain. These investigators have approached the problem from an immunologic standpoint and have suggested that in certain instances chronic thyroiditis may result from autoimmunization of the patient to his own thyroglobulin. One outcome of these studies has been an increasing awareness of the incidence of the disease and the possibility of diagnosing it by clinical and laboratory methods. Furthermore, it has been urged that, since operation is unnecessary for its diagnosis, all need for surgical intervention is obviated and the disease is best treated by conservative medical measures. That this laudable aim is not without certain drawbacks is suggested by the following studies.

MATERIAL

Records of all patients operated on for chronic thyroiditis by various staff members at Sacred Heart Hospital between January 1, 1951 and December 31, 1959 were reviewed. Histologic slides on representative cases and unusual cases were re-examined. Evaluation of symptoms and physical findings was carried out in an effort to detect distinguishing features.

RESULTS

During the 9 year period encompassed, 1,682 thyroidectomies were performed. In 189 of these the diagnosis of chronic thyroiditis was made. There were 103 cases of Hashimoto's disease, 48 cases in which diffuse but atypical or ligneous thyroiditis occurred, and 38 instances of focal thyroiditis. The incidence per year is shown in Figure 1. It will be noted that the number of operations carried out for chronic diffuse thyroiditis rose from less than 2 per cent in 1951 to over 12 per cent in some of the later years of the study, the greatest increase occurring in Hashimoto's disease. The most startling finding is the occurrence of 9 carcinomas in association with Hashimoto's disease, 8 of them seen in the last 3 years. Thus, 8.7 per cent of all patients undergoing thyroidectomy for Hashimoto's disease were found to have associated carcinoma, and Hashimoto's disease was present in 8.1 per cent of all patients operated on for carcinoma of the thyroid. Figures 2 through 6 indicate representative sections from 2 of these cases. It should be emphasized that carcinomatous glands with an associated inflammatory reaction were carefully excluded and that only those glands were considered in which the predominant pathologic changes were those of Hashimoto's disease, the carcinoma being an incidental finding. The over-all incidence of carcinoma among the 1,682 goiters removed was 111 or 6.6 per cent.

A comparison of the patients with uncomplicated Hashimoto's disease and those with associated carcinoma was made in an effort to determine whether there were any distinguishing features. There were 88 females and 6 males in the Hashimoto's group, 8 females and 1 male in the carcinoma group. Patients ranged from 10 to 69 years of age, averaging 36.6 years in the Hashimoto's group, and from 27 to 66, averaging 45.3 years in the carcinoma group. One patient in the carcinoma group had a positive family history for carcinoma of the

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thyroid. Duration of the goiter in the Hashimoto's group was a matter of weeks in 7 patients, months in 36, and years in 33. The enlargement of the gland was first noted on physical examination in 13 instances. In the carcinoma group a number of the patients had had subjective symptoms for several months; however, in 7 of the 9, the presence of goiter was detected by the patient's physician. Seven of the patients in the Hashimoto's group had had a previous operation; 1 had had roentgenotherapy. None of the patients in the carcinoma group had had either of these therapeutic modalities. Four patients in the Hashimoto's group had a history of previous subacute thyroiditis as did 1 patient in the carcinoma group. Twenty-six patients in the Hashimoto's group had pressure symptoms, 2 of the patients with carcinoma. Fourteen patients with Hashimoto's disease had pain or tenderness, whereas none of the patients with carcinoma complained of these symptoms. Twenty-five of the patients with Hashimoto's disease were thought to be mildly toxic, 2 of the patients in the carcinoma group. The gland was described as hard or firm in 30 of the patients with Hashimoto's disease, and carcinoma was suspected in 10. There were 4 patients in the carcinoma group in whom the gland was hard, but in only 1 of the patients in this group was carcinoma remotely suspected before operation. Basal metabolic rates and radioactive iodine uptakes were not determined frequently, but when they were, with 3 exceptions, they were either normal or subnormal. Preoperative diagnosis in the Hashimoto's group was nodular goiter in 40 patients, diffuse goiter in 10, solitary adenoma in 20, and thyroiditis in 15. Preoperative diagnosis in the carcinoma group was nodular goiter in 3 patients, solitary adenoma in 4, thyroiditis in 1, and tumor in 1. Operative procedures carried out in the Hashimoto's group were total thyroidectomy in 3, subtotal in 62, total lobectomy and resection of the opposite lobe in 8, lobectomy alone in 9, and resection of one lobe and

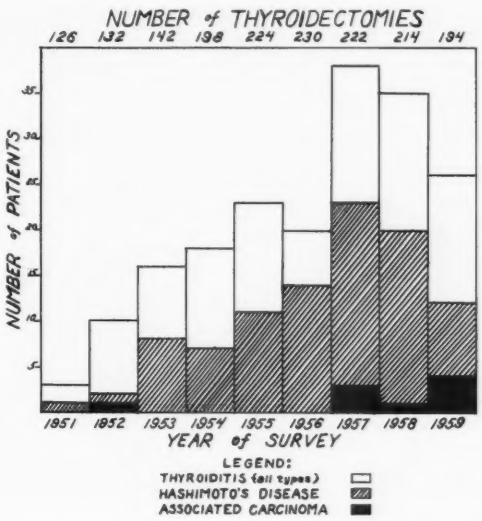

FIG. 1. Incidence of thyroiditis and carcinoma among patients undergoing thyroidectomy.

the isthmus in 12. In the carcinoma group total thyroidectomy was carried out 3 times, in 1 case in 2 stages, subtotal thyroidectomy 2 times, and total lobectomy and resection of the opposite lobe, 4 times. No radical neck dissections were carried out, although, in 4 patients with carcinoma, regional lymph nodes were removed for pathologic study.

Pathologic study revealed 81 cases of uncomplicated Hashimoto's disease, 6 cases in which solitary nodules were present, 6 cases in which the condition was associated with nodular goiter, and 1 instance in which diffuse parenchymatous hypertrophy was present. In the carcinoma group, all patients showed changes characteristic of diffuse Hashimoto's disease. In addition to these changes there were 3 follicular adenocarcinomas, grade 1, 5 papillary carcinomas, grade 2, and 1 diffuse adenocarcinoma. In 2 patients the tumor was multicentric, and in the remaining 7 the malignant area was small and localized. All of the neoplasms were well differentiated, and in only 1 instance was angioinvasion demonstrable. There was no evidence of metastasis in the 5 patients in whom lymph nodes were ex-

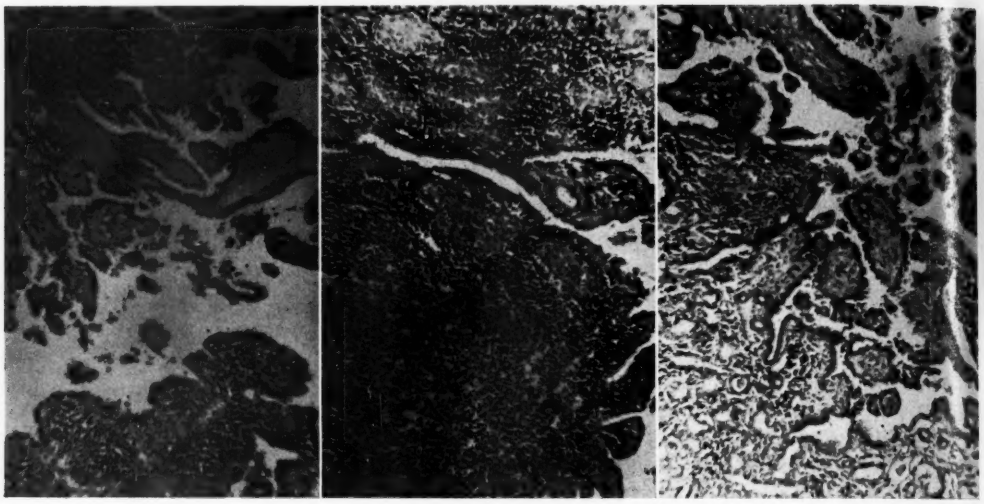

FIG. 2. FIG. 3. FIG. 4.

FIGS. 2, 3, and 4. Thyroid tissue from 45 year old, white female, showing a typical mixed papillary and follicular adenocarcinoma. Note lymphocytic infiltrate with follicles extending into the tumor from a surrounding struma lymphomatosa. The remainder of this gland showed a typical diffuse Hashimoto's disease. Total weight of resection, 20 grams. These sections are taken from a nodule 1.5 centimeters in diameter found in the right lobe. Hematoxylin and eosin, ×68.

amined. There were no postoperative deaths. Complications in the Hashimoto's group included mild hemorrhage in 5 cases, wound infection in 1 case in which an esophageal diverticulum was removed at the same time, atelectasis in 1 case, and 1 case of upper respiratory infection. In 1 patient in the carcinoma group auricular fibrillation and angina developed. The amount of tissue removed at operation ranged in weight from 1.5 to 131 grams, the vast majority of specimens weighing less than 30 grams, within the Hashimoto's group, and from 15 to 73 grams with an average of 28.2 grams in the carcinoma group.

COMMENT

Early reports of malignant tumors in association with Hashimoto's disease were for the most part limited to malignant lymphomas and fibrosarcomas. However, in the last decade a few reports have appeared concerning the simultaneous occurrence of thyroiditis and carcinoma. Interestingly enough, one of these was by Crile and Fisher who have been staunch proponents of nonoperative treatment of thyroiditis. The most exhaustive investigations have been those of Lindsay and Dailey and their associates (2, 5), but Howard and Pollack and Sprong also have pointed out the frequency with which carcinoma may be found in chronic thyroiditis. The impossibility of determining clinically which patients with thyroiditis also have carcinoma has been emphasized by these writers as has the fallibility of needle biopsy and even of frozen section. This has been borne out by our studies. Both conditions occur almost exclusively in females, the patients with carcinoma tending to be a decade older. In general, symptoms were of shorter duration and the goiter was apt to be discovered by the patient's physician in the carcinoma group. About 1 of 4 patients had pressure symptoms in each group and a comparable number had symptoms suggesting thyrotoxicosis, an impression which, however, was not supported by thyroid function tests when performed. The firmness, which was

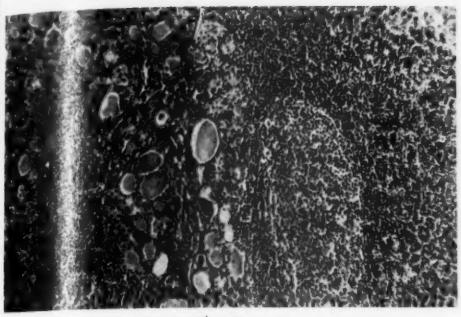

FIG. 5.

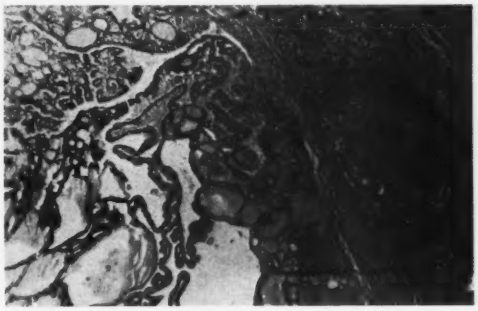

FIG. 6.

FIG. 5. Typical Hashimoto's disease in a 54 year old white male showing active follicle formation. Total weight of resection 24 grams. Hematoxylin and eosin, ×63.

FIG. 6. Nidus of moderately well differentiated papillary adenocarcinoma of the thyroid from the same patient as shown in Figure 4, found as a small nodule in the right lobe, 0.8 centimeter in diameter. Hematoxylin and eosin, ×63.

a prominent finding in Hashimoto's disease, was not helpful in the detection of the associated carcinoma. It was a little depressing to see how seldom even thyroiditis was suspected preoperatively, and, although carcinoma was occasionally suspected in the patients with Hashimoto's disease alone, it was suspected in only a single patient who also had a carcinoma. Carcinomas which were found tended to be well differentiated, a factor contributing to the favorable prognosis noted by others as well as ourselves. None of our patients had metastasis to regional lymph nodes, although others have found the regional lymph nodes frequently involved.

It seems to us, since operative treatment can be carried out with minimal risk, that it is hard to justify conservative treatment in chronic thyroiditis, in view of the ever present danger of an associated malignant tumor within the diseased thyroid gland.

The use of steroid compounds, so helpful in patients with subacute thyroiditis, is of little value in chronic thyroiditis. On experimental and clinical grounds, the use of any type of roentgen irradiation or of thiourea compounds would appear to increase the hazards of malignant degeneration. The most widely used form of conservative treatment, the administration of desiccated thyroid, may reduce the size of the goiter and correct the associated hypothyroidism but does not alter the histology in Hashimoto's disease and offers no protection against the very real danger of unsuspected carcinoma.

Pollock and Sprong, who reported an 11 per cent incidence of malignant tumors in 52 cases of Hashimoto's disease, state that the compelling indication for surgical intervention is the considerable chance of malignancy. Piercy thought it likely that all lymphadenoid goiters should be removed on this indication.

The increasing incidence of thyroiditis and its appearance in a younger age group than formerly warrant comment. Twelve of our patients with Hashimoto's disease were under the age of 20 years. So far, despite the new concepts of pathogenesis, there is no explanation for these trends. Pathologic changes, similar to those seen in Hashimoto's disease, are often seen after irradiation of a hyperplastic gland or experimentally after immunization of an animal against thyroglobulin; yet what initiates these changes in Hashimoto's disease remains obscure. Whether our present diversified diet or other environmental influences are contributing factors is unknown, since no one has shown that either goitrogens or deficiency states play a role in the production of thyroiditis. Lindsey and Dailey (4) and Thompson have emphasized that in

thyroiditis, although lymphoid changes predominate, the primary alteration occurs in the epithelium, and both degeneration and overgrowth can be found. What the effect of the high level of unopposed thyrotropic hormone on these deranged cells may be is problematical. As the number of parenchymal cells gradually decreases during the progress of Hashimoto's disease, the production of thyroid hormone diminishes. As a result there is ever less antagonism to the production of thyrotropic hormone by the pituitary which, in turn, can further stimulate any remaining thyroid cells, possibly even to neoplasia.

SUMMARY

A review of 189 patients undergoing thyroidectomy for chronic thyroiditis during the past 9 years has been presented. One hundred and three of these patients had Hashimoto's disease and, of these, 9 had associated carcinoma of the thyroid gland. In view of these findings it is suggested that the conservative treatment of chronic thyroiditis is ill advised.

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A PRIMARY COMPROMISE FOR BILATERAL CLEFT LIP

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THERE MUST BE few experiences more horrifying than the parents' first view of their newborn infant disfigured by a bilateral cleft of the lip. The arrival of this deformed baby is a tragic climax to 9 months of happy anticipation, and to bring the news to the parents is indeed an unenviable task for the obstetrician. The parents' despair and the infant's future demand of the surgeon a continued and never-ending search for improvement in the construction. Yet there must be caution, for whatever operation is executed during the early months will influence this face throughout life. The vital importance of the surgeon's role is magnified when the infant is otherwise normal, for his chance of happiness hangs heavily not only on the functional but also on the cosmetic correction of the deformity.

FRONTONASAL DISCREPANCY

The difficulty of this deformity is the bilateral absence of parts plus the severe distortion of what is present. Formidable is the task of making up the missing and repositioning the distorted. Bilateral clefts, in addition to the actual clefts and absence of a cupid's bow remnant, also have a varying degree of vertical shortness in what is referred to embryologically as the frontonasal component. This is measured from a position at the nasal tip to the midinferior point of the free border of the prolabium of the upper lip. The discrepancy may lie in the prolabial length, the columella length, or a combined shortness in both. Due to this shortness an age old tug of war continues to wage in which the prolabium is being pulled from both below and above. Some surgeons drag the prolabium down into the lip with little regard for the sanctity of the nasal tip (Fig. 1a), whereas others haul it up into the columella, suturing the lip together tightly beneath it (Fig. 1 b). Each maneuver has strong pull for its side which insures against either being the undisputed winner. Thus a compromise has been devised by the author with primary respect for both the lip and the nose.

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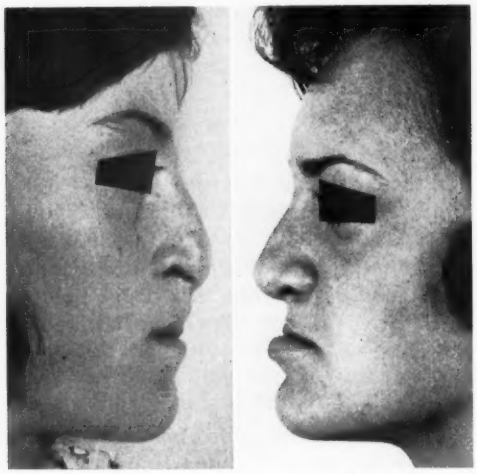
GUIDED BY PRINCIPLE

The conservative approach which merely freshens the edges of the cleft and the prolabium and joins them surgically is still popular, does little damage, and is sound as far as it goes. Yet to procrastinate in the hope that time and growth will further correct the congenital discrepancy is wishful thinking. Nature did not provide for it from the beginning and has minimal intention of making up the shortage. Thus we must turn to certain of the principles of plastic surgery. When tissue is actually missing it is a sound and proved principle that only by introducing new tissue can an adequate correction be achieved. The choice of the new tissue to be used is influenced by another plastic principle. Borrow from Peter to pay Paul only when Peter can afford it.

INCOMPLETE BILATERAL CLEFTS

In bilateral incomplete clefts the columella is usually of adequate length and the nasal tip is in normal position. The discrepancy in vertical frontonasal length lies in the shortness of the prolabium. The common approach toward correction of this discrepancy has been the use of various shaped flaps from the lateral lip elements which, when stuck to the lower border of the prolabium, bolster this short center component. Techniques utilizing this principle have been described by Koenig, Maas, Rose, and Thompson, Barsky, Veau, Padgett and Stephenson, LeMesurier, Stenstrom, and



a b

FIG. 1. a, Incorporation of the total prolabium into the lip in the presence of a short columella pulls the nasal tip down. b, Incorporation of the prolabium into the columella area may avoid a flat nasal tip but is usually responsible for tightness of the upper lip.

Kahn and Winsten. This approach often produces a lip that is too long in its vertical dimension and of course must produce cross scars in the lower middle lip which spoil any attempt at a natural philtrum effect.

A logical approach would seem to be division of the short prolabium from the normal nose component so that it can be moved down into the natural philtrum position in the lip. Maintenance of this correction can be achieved by advancement of lateral lip flaps into the gap between columella and prolabium. In order to preserve prolabial blood supply, this maneuver will require two stages (Fig. 2). First one side of the prolabium is freed from the columella by a rotation incision and into the gap is advanced the triangular flap from the lateral lip element similar to the rotation-advancement principle in unilateral lip clefts, as described previously (13). A wedge from the nostril floor facilitates the advancement.

As bilateral clefts possess no remnant of a cupid's bow, one must be created. Vermilion mucosa bordering the cleft edge of the lateral lip element is turned down as a flap. One-half of the inferior prolabium vermilion mucosa is also turned down and onto this is overlapped the lateral vermilion flap to form one-half of a cupid's bow (Fig. 2 a and b). One month later a similar rotation, advancement, and vermilion mucosa overlap is carried out (Fig. 2 c and d). This will achieve a complete cupid's bow, a normal nose, and a prolabium posing as a philtrum with the scars of union running along philtrum column lines as shown in Figure 3.

When the bilateral cleft is complete on one side and incomplete on the other, then the same rotation, advancement, and vermilion overlap is carried out and again in two stages. The order of closure is important. Priority must go to the complete cleft, as the attachment to the lateral lip element on the incomplete cleft side will maintain the blood supply of the prolabium.

COMPLETE BILATERAL CLEFTS

Complete bilateral clefts pose three additional problems which are not usually encountered in incomplete clefts: (1) a protruding premaxilla, (2) inadequacy or absence of the columella, and (3) sole source of blood supply to the prolabium through the columella and premaxilla.

PROTRUDING PREMAXILLA

When the cleft is complete bilaterally, the premaxilla is attached to the face only by the septum and columella. The premaxilla, when unattached to the maxilla, may protrude on a septal stalk varying distances out in front of its usual position in the alveolar arch. There is justified controversy as to what to do with this jutting premaxilla. Some favor septal resection, premaxilla pushback, and fixation into the alveolar arch in severe cases, whereas others oppose this approach, believing that such action retards normal growth. For the present a compromise is preferable. If the premaxilla is well in the arch, then by turning mucosal flaps a fibrous union can be achieved. If the premaxilla is jutting far out on the end of

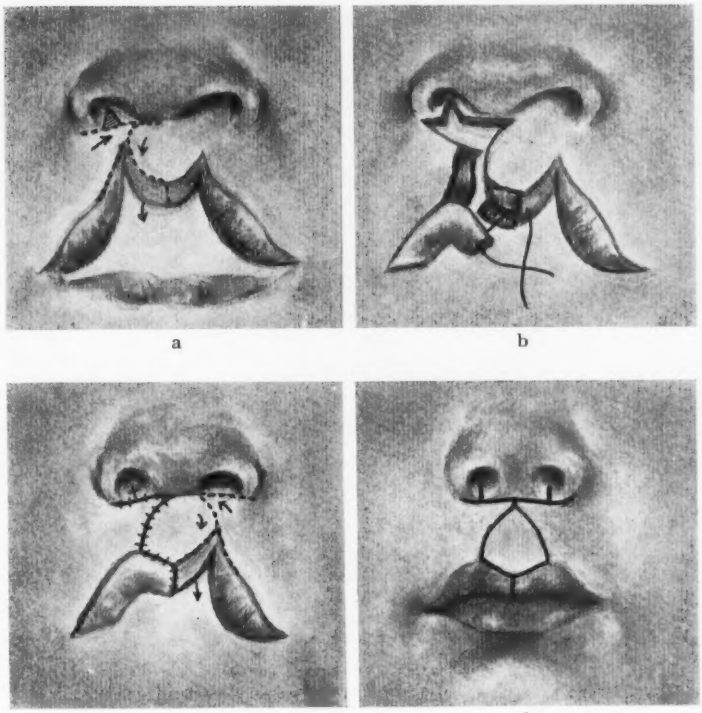


FIG. 2. Alternate method of correcting incomplete bilateral cleft with typical short prolabium. a and b, Mark and cut rotation incision to drop one-half of the prolabium. Then advance a triangle flap from the lateral lip element to fill the gap. A wedge from a relatively wide nostril floor facilitates advancement. Turn-down of the prolabium vermilion is overlapped by lateral vermilion to form half of a cupid's bow. c, Sutured result on one side shown; marked plan on opposite side to be executed 1 month later. d, Healed scar lines show prolabium in new philtrum position.

the nose, then a septal resection, which is designed to affect growth as little as possible and still let the premaxilla back in the arch, seems warranted. Between these extremes are premaxillas protruding varying distances, and many can be maneuvered successfully by lip moulding and orthodontics. The prosthodontic technique of early "stimulation" of the maxillas by prosthesis until they are in alignment with the protruding premaxilla might alleviate the necessity of septal resection, as Burston has indicated. This seems an ideal approach in theory but late results must be seen and evaluated.

SHORT COLUMELLA

In complete bilateral clefts the prolabium may or may not be short but the discrepancy in vertical frontonasal length is often seen in the inadequacy or absence of columella. To use the entire prolabium as columella lifts the nasal tip but is unacceptable as it leaves the lip without a philtrum. To incorporate the prolabium in the lip has obvious labial advantages but in the process pulls the nasal tip flat. In spite of this nasal disadvantage the prolabium-into-lip approach is considered embryologically sound by Stark and Ehrmann and is favored by Adams and Adams, Axhausen, Brophy, D. Browne, J. B.

a b

FIG. 3. Incomplete bilateral cleft. a, Columella is adequate but prolabium is short. b, Result of bilateral rotation, advancement, and vermilion overlap in two stages.

Brown, Schultz, Federspeil, Vaughn, and Cronin. Then at 5 to 17 years of age some type of columella lengthening procedure is called upon in an attempt to correct the flat nose. To lengthen this type of short columella the forked flap was devised by Millard (14). Since then it has been used successfully in a number of primary bilateral cleft lip closures. The proposition is a compromise using the principle of borrowing from Peter to pay Paul. Peter is the prolabium which can just afford what Paul, the columella, needs and still retain enough for himself as the prolabial philtrum of the lip. The forked flap's function is primarily a columella lengthening procedure. Each prong of the flap is continuous with the columella base and picks up one vertical cleft scar and as much prolabium as will give sufficient body for a columella and still leave a natural looking philtrum. The prongs of the forked flap are sutured together and with the aid of a through and through horizontal membranous septal incision this unit is advanced as additional columella to free the tip of the nose. As in other columella lengthening procedures utilizing portions of the upper lip in males there may or may not be a few hairs surviving in the lower part of the columella. This has not been a serious problem.

PROLABIUM BLOOD SUPPLY

The discrepancy in frontonasal length may be shortness in prolabium, columella, or both. Thus in principle, just as in incomplete clefts, the prolabium must be divided from the columella and new tissue inserted to make up the shortage. Yet the sole blood supply to the prolabium comes from the columella and to a lesser degree from the premaxilla. This anatomic situation dictates that not only must the division be carried out in at least two stages but also that a new blood supply must be brought in from the sides to maintain a viable prolabium.

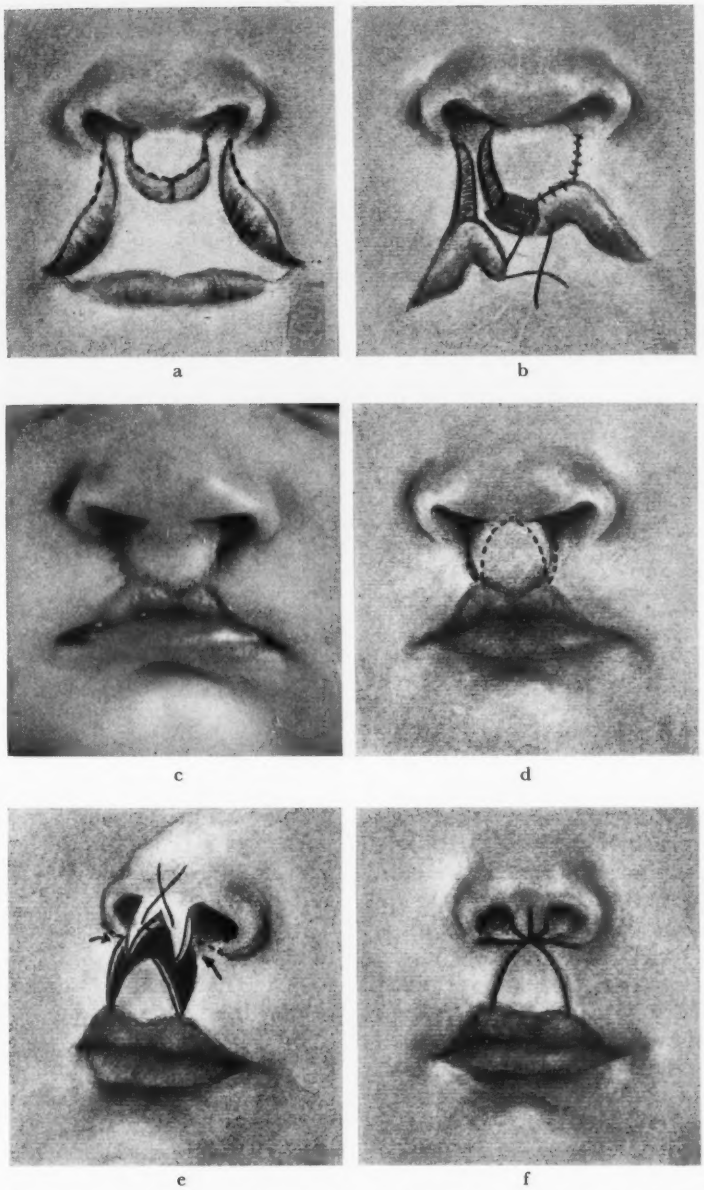


FIG. 4. Alternate method of correcting complete bilateral cleft with protruding premaxilla, short prolabium, and absent columella. a, Mark vermilion for turndown flap from prolabium and overlap flap from lateral lip. b, Lateral lip joined to side of prolabium. c, Photograph of healed first stage of patient shown in Figure 5. Blood supply to prolabium is now also coming from lateral vermilion flap attachments. d, Mark delay of forked flap taking bilateral scars and lateral portions of the prolabium. e, Lifting and suturing the forked flap raises the nasal tip as it lengthens the columella. Lateral lip flaps are advanced to join the reduced prolabium philtrum. f, This compromise has lengthened the columella, narrowed the nasal flare, and tailored the prolabium.

a b c

FIG. 5. a, Complete bilateral cleft with protruding premaxilla, absence of columella, and alveolar defect without cleft palate. Septal resection allowed premaxilla to fit into alveolar notch. Figure 4c shows lateral elements attached to prolabium in first stage. b, Completion of forked flap showing nasal tip elevation. c, Alar flare has been minimized. Prolabium is serving as a natural philtrum and is bordered inferiorly by a vermilion cupid's bow.

OPERATIVE STAGES

1. When early "stimulation" by prosthesis is planned by the dental team, operation can be postponed as long as is necessary. If the premaxilla is to be put back into the alveolar arch it can be done at 1 month of age when the first stage of the lip closure usually is performed. A vermilion flap is turned down from the inferior edge of the prolabium to form lining. Then a vermilion flap from each lateral lip element is brought across to overlap the prolabium vermilion and form a cupid's bow. This also brings in a new permanent blood supply to the inferior edge of the prolabium. The sides of the prolabium can be freshened and joined to the lateral lip elements in the usual manner (Fig. 4a, b, and c).

2. The second stage is optional but is suggested as a safety delay after 1 month. The prolabium attachment to the premaxilla is divided. At the same time, the medial incisions for the forked flap are made as an inverted V with the apex at the columella base (Fig. 4d).

3. Two weeks later the forked flap including in each prong one bilateral scar and a portion of a prolabium, is lifted out of the lip (Fig. 4e). These prongs are sutured together as an extension of the columella. Then, with the aid of a membranous septal incision which curves over the tip of the septum, the flat nasal tip is freed and the new columella is advanced and sutured into position.

The reduced prolabium with its lateral edges freshened is now completely free from the nasal attachments. It is, in fact, suspended by the vermilion mucosal bridges forming its cupid's bow. Curved transverse incisions along the upper edge of each lateral lip element which swing under each alar base develop two triangular flaps similar to those used in incomplete bilateral as well as unilateral clefts (Fig. 4e). When these flaps are advanced tip to tip over the

prolabium they rotate the flaring alar bases in and narrow the wide nostril floors. This places the tailored prolabium in the natural position of a philtrum (Fig. 4f and Fig. 5). Very fine suture material is used for all closures, No. 5-0 chromic catgut for mucous membrane, No. 6-0 chromic catgut for muscle and vermilion flaps, and No. 6-0 silk or preferably mersilene for skin. The skin sutures are kept covered with bacitracin ointment during the 4 days which they are retained in order to protect the stitch line from nasal discharge.

SUMMARY

The discrepancy in vertical frontonasal length in bilateral lip clefts requires introduction of new tissue to make up the shortage. In incomplete bilateral clefts division of the prolabium from the columella can be maintained by advancement of triangular flaps from the lateral lip elements. This allows migration of the prolabium into a natural philtrum position. In complete bilateral clefts the shortage is also seen in the columella. The prolabium becomes the site of a compromise as a forked flap is lifted from its sides to lengthen the columella and lift the flat nasal tip. This action radically freshens the sides of the prolabium to receive the triangular flaps to be advanced from the lateral lip elements. The final result gives a free nasal tip, lengthened columella, narrowed alar flares and nostril floors, and a more natural prolabium philtrum with union scars running as philtrum columns. This method of freeing the nasal tip early by releasing the drag of a short columella should encourage rather than discourage normal nasal growth.

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THE AURICULOTEMPORAL (FREY) SYNDROME OCCURRING AFTER PAROTID SURGERY

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THE AURICULOTEMPORAL or Frey syndrome, as it is called also, consists of ipsilateral redness and sweating of the face, often over the temporal and preauricular regions, evoked by eating. It is a sequel of penetrating wounds, surgical incisions, or suppuration in the region of the parotid gland and may follow injury to the cervical or upper thoracic portions of the sympathetic trunk.

More patients who manifest these symptoms are being encountered because of the marked increase in the frequency of parotidectomy at our institution. This fact stimulated us to review the literature and to call attention to this syndrome with special reference to its occurrence after operation on the parotid gland.

Baillarger, who described in 1853 the phenomenon of gustatory sweating over the cheek during eating, is given credit by Pfeffer and Gellis for presenting the earliest case of auriculotemporal syndrome. We will consider briefly only a few of the other articles of historical import. The reader is referred to Goatcher, Langenskiöld, and Pfeffer and Gellis for more details and references. In 1897 Parke-Weber described a young boy who, after a suppurating lesion in the region of his left parotid gland, had sweating and flushing on that side of his face when he ate. Because the area involved corresponded to the distribution of the auriculotemporal nerve, Parke-Weber referred to the condition as the auriculotemporal syndrome.

Frey, who did substantial work on the subject, described this condition again in 1923 in a patient who had parotitis secondary to a gunshot wound of the face. The condition later became known as the Frey syndrome.

The condition was reported after suppurative parotitis mainly secondary to typhus or typhoid fever in 14 cases in 1926 and after syringomyelia and mumps by Wilson in 1936. List and Peet, Payne, and Freedberg and associates, among others, found the syndrome a sequel to parotitis. Pfeffer and Gellis in 1951 reported it in a newborn child after incision and drainage of a parotid abscess. Goatcher in 1954 recorded it after superficial parotidectomy for chronic parotitis, and Coldwater in 1954 reported marked relief in 2 cases by resection of the auriculotemporal nerve with anastomotic branches from the facial nerve.

ETIOLOGY

All investigators writing of this syndrome have begun their comments on etiology by saying that it is not completely understood. Even Laage-Hellman was modest enough to say that "its aetiology does not seem to be perfectly understood," although his experiments should leave little doubt concerning the cause.

The syndrome is mediated through the auriculotemporal nerve which arises from the posterior division of the mandibular nerve and enters the parotid area between the ear and the condyle of the mandible. The nerve courses deep to the parotid gland and anastomoses with the facial nerve before becoming superficial to provide the sensory supply to the skin of the temple, the

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anterior parts of the ear, and part of the cheek. By way of the otic ganglion, the auriculotemporal nerve receives parotid secretory fibers from the glossopharyngeal nerve. It also receives sympathetic sudomotor and vasomotor fibers derived from the cervical sympathetic ganglia via the external carotid plexus. The sweat glands of the face are innervated by the cervical sympathetic outflow, the postganglionic fibers of which are distributed with the peripheral branches of the trigeminal nerve. Sweating of the face in response to heat is mediated by the sympathetic pathways as has been regularly demonstrated by the absence of sweating in response to heat in the face after cervical sympathetic ganglionectomy. The sudomotor sympathetic nerve endings, contrary to the general rule, are cholinergic rather than adrenergic. It has been suggested repeatedly, but not unequivocably proved, that the sweat glands of the face are also innervated parasympathetically, according to Langenskiöld and Wende and Busch.

Certain individuals have a normal gustatory sudorific reflex that is usually brought on by highly spiced or acid foods, according to Pfeffer and Gellis. The relation of this unusual physiologic response to the auriculotemporal syndrome is hypothetical but suggestive. Some individuals at least must have a physiologically active mechanism which produces facial sweating in response to gustatory stimulation.

The basic mechanism of this syndrome has been the subject of considerable speculation. The most plausible theories advanced to explain the mechanism of gustatory sweating are those based on the principle that sweat glands are reactivated after a period of paralysis due to denervation. Laage-Hellman listed three plausible ways in which a denervated sweat gland may be reactivated, namely, (1) hypersensitivity to a chemical transmitter substance after denervation (denervation hypersensitivity), (2) regeneration of the normal nerve supply, and (3) reinnervation by salivary fibers.

Hypothesis 1. Langenskiöld, in 1946, Haxton, and Freedberg and associates in 1948 stated that the mechanism of the syndrome is related to a denervation hypersensitivity of the sweat glands which occurs after injury to the parotid region. They found pronounced hypersensitivity to acetylcholine in the skin of the affected region and deduced from this that the local mechanism was a humoral one, the acetylcholine liberated at the endings of the cholinergic nerve acting on the sensitized end organs in the skin. The source of the liberated acetylcholine was conjectural, but they apparently considered that it was liberated by the salivary gland during its activity which is a parasympathetic function.

Hypothesis 2. List and Peet suggested that the sweating phenomenon results from diffusion of acetylcholine or cholinergic substances from the injured parotid gland. The spread of the reaction, the distribution over the entire course of the auriculotemporal nerve, and the occurrence of the phenomenon in patients whose parotid gland has been completely destroyed are against this interpretation.

Needles noted the appearance of the auriculotemporal syndrome on closure of a salivary fistula and expressed the opinion that the syndrome might be caused by the irritation of sudomotor fibers passing through or near the parotid gland by the swelling of the gland on mastication. As the syndrome may appear in the presence of an atrophied parotid gland, this theory appears unlikely.

Frey considered the reflex as essentially normal but that it had been accentuated through injury to the auriculotemporal nerve with subsequent irritation of vasodilator fibers in the cicatrix of the sclerotic parotid gland. In that way she incriminated scar tissue.

Hypothesis 3. André-Thomas, Ford and Woodhall, and Payne suggested that the auriculotemporal syndrome might result from misdirected regeneration of nerve fibers. Since each proximal nerve stump regenerates by growing a "brush" of neuro-

TABLE I.—REPORT OF CASES OF AURICULOTEMPORAL SYNDROME AFTER PAROTIDECTOMY

Case	*Age, yrs., and sex*	*Operation*	*Pathologic findings*	*Sweating*	*Hyperemia*	*Pain*	*Onset postop., mos.*
1	25M	Left subtotal parotidectomy	Mixed tumor	+	+	0	12
2	59F	Left subtotal parotidectomy	Adenocarcinoma, grade 1 (cylindroma)	+	+	0	12
3	68F	Right subtotal parotidectomy	Mucoepidermoid carcinoma	+	+	+	2
4	40M	Right subtotal parotidectomy	Hyperplastic lymph node	+	+	+	18
5	66F	Left subtotal parotidectomy	Mixed tumor	+	+	0	9
6	46F	Right total parotidectomy with preservation of facial nerve; right radical mastoidectomy	Cylindroma of external auditory canal	+	+	0	3
7	54M	Right total parotidectomy with preservation of upper division of facial nerve; nerve graft to lower division of facial nerve	Adenocarcinoma	+	+	0	12
8	68F	Left partial parotidectomy	Adenocarcinoma, grade 2	+	+	+	12
9	67F	Right total parotidectomy preserving facial nerve; right radical dissection of glands of neck	Squamous cell epithelioma, grade 3	+	+	0	6
10	50F	Left subtotal parotidectomy	Chronic sialadenitis	+	+	+	4
11	60M	Left subtotal parotidectomy	Warthin's tumor	+	+	0	10

fibrils down the peripheral segment of several neurons, they reasoned that some salivary secretory fibers could grow along the course of sudorific fibers and innervate sweat glands after regeneration is completed. The latent period before development of the syndrome would coincide with the period during which regeneration is taking place.

This hypothesis is the most plausible, as shown by Laage-Hellman's studies. He demonstrated that denervation of the sweat glands follows trauma; hence the altered dermal sensation indicates that the auriculotemporal nerve has been damaged and that an opportunity for misdirected regeneration of salivary fibers has occurred. Both sweat glands and salivary glands are cholinergic so that the regenerated fiber and its new effector organ would not be incompatible. Laage-Hellman expressed the view that critics of this theory base their objection on too short a latent period, and that such critics have used inadequate criteria in estimating the duration of the latent period. To him the permanent nature of the syndrome indicated that a new pathway has been established and that objective tests on those patients who claim that the pathway has disappeared will show that it is still present.

INCIDENCE

The most accurate figures on the actual occurrence of this syndrome must be Laage-Hellman's because of his systematic, continuous, and objective follow-up of patients who had undergone parotidectomy.

Although only 100 cases of this condition have been reported in the literature, it undoubtedly has occurred much more frequently and has been unrecognized, unreported, or erroneously diagnosed as due to a salivary fistula. It is seen commonly in clinics where a large number of operations are performed on the head and neck. Hayes Martin in a personal communication estimated that it occurs in about 10 per cent of the patients who undergo operations on the parotid gland. According to Laage-Hellman, this syndrome appears regularly after conservative parotidectomy if objective tests are

performed. Sixty per cent of the patients affected are aware of the symptoms and only 13 per cent feel distress.

DATA ON CASES STUDIED

Data on 11 patients treated at the Mayo Clinic between 1951 and 1957 for the auriculotemporal syndrome after operation on the parotid gland are given in Table I. These 11 patients were taken at random and do not represent all of the patients who had this syndrome after operations on the parotid gland during the interval under consideration. The group includes some patients who complained of the syndrome and others who were asked if they had noticed the symptoms. The data recorded represent information received in retrospect and are for the most part subjective.

The cardinal signs of hyperemia (flushing) and sweating were seen in all of our patients and were precipitated by eating. Any type of food would precipitate the symptoms, but spicy foods particularly stimulated it. Pfeffer and Gellis said that any stimulus to salivation is sufficient to precipitate this response. Erythema generally appeared after chewing for 1 minute or less, and sweating followed shortly thereafter; the reaction continued unchanged for the duration of the chewing and faded away within a few minutes after chewing was stopped. Slight to moderately severe pain in the distribution of the auriculotemporal nerve was noted by 4 of these patients. Pfeffer and Gellis stated that the pain may be severe.

A latent period of 2 to 18 months followed operation on the parotid gland in our cases before appearance of the syndrome; the average interval was about 9 months. Once the typical gustatory response was noted, no improvement can be expected, as indicated by the reports of List and Peet and Freedberg and associates. Some of their patients followed up for 40 years have not shown any change. In some of our cases the flushing preceded the sweating by several months or years. Physical examination of the face showed numbness in the area of distribution of the auriculotemporal nerve in 3 of these patients. Hyperesthesia was found in some.

TREATMENT

Since the auriculotemporal syndrome is benign, an accurate diagnosis can be a source of great satisfaction to the patient. Reassurance and explanation usually suffice with regard to therapy. We have had no experience with resection of the auriculotemporal nerve for the relief of this syndrome. Parotidectomy must include resection of the auriculotemporal nerve and therefore it is not reasonable to make a special attempt to seek out the nerve and deliberately try to resect part of it. Laage-Hellman has shown that such resection does not prevent the appearance of the syndrome. Resection of the nerve as a secondary procedure after parotidectomy may be associated with the risk of injuring the facial nerve because of the altered anatomy and scar present in the operative field. It has not been shown that the results from such an operation will be permanent.

Roentgen-ray treatment to the skin involved can produce permanent results only if enough irradiation is given to the sweat glands to cause atrophy. There seems to be no reason for such drastic action.

If the area of sweating is small enough, it can be excised. This circumstance must be rare. Intracranial division of the glossopharyngeal nerve seems to be impractical and so is oral treatment with anticholinergic agents. Laage-Hellman suggested topical treatment with an anticholinergic agent in a cream. A cream that is 3 per cent scopolamine hyperbromide is effective in alleviating the symptoms.

SUMMARY

The so-called Frey or auriculotemporal syndrome is characterized by sweating and flushing of the face which are evoked by eating. This syndrome occurs regularly after parotidectomy, but only 10 to 15 per cent of those affected will feel distress.

The primary cause is a lesion in a region containing salivary and sweat gland fibers. It is mediated by the same reflex arc as is gustatory salivation, through the auriculotemporal nerve. The dermal sensation in the area is altered, and thermoregulatory sweating is diminished. The affected area usually shows increased sweating after injections of cholinergic agents. The first signs of the syndrome appear approximately 8 weeks after trauma (denervation) to the regular pathways; the syndrome is permanent. The basic mechanism is due to a misdirected regeneration of salivary nerve fibers.

Reassurance and explanation practically always will suffice as treatment. Topical treatment with an anticholinergic agent should be considered a promising and most practical method of treatment.

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BLOOD VOLUME CHANGES ASSOCIATED WITH ESSENTIAL HYPERTENSION

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THE THERAPY of essential hypertension has within recent years been modified by the use of surgical procedures, particularly in those patients who are refractory to medical therapy. Sympathectomy and, more recently, subtotal or total adrenalectomy and sympathectomy have been effective in the treatment of these patients. The favorable results of this latter surgical management have been reported previously (1, 9) and will not be discussed in this report.

The blood volume of hypertensive patients has been studied previously by many investigators with a wide variation in the findings. Rusznyak reported in 1927 and Walser and associates in 1956 that blood volumes of hypertensive patients were decreased. Davis and Mayerson in 1948 reported that the blood volume of hypertensive patients was the same or less than that of normotensive patients. Harris and Gibson in 1939 and Reilly and associates in 1954 reported essentially the same results. Gunton and Paul and Eisenberg showed that, if the blood volume was increased in any of the patients studied, this measurement correlated with the degree of congestive failure present at the time of measurement. They also noted that when cardiac compensation had been restored, the blood volume returned to normal levels.

The variability of these results was in part due to the small numbers of patients studied in any series, and apparently neither cardiac failure nor renal azotemia was considered as a factor which might increase the blood volume independently with the changes associated with hypertension. Thus, some previous series have not differentiated between complicated and uncomplicated severe hypertension.

A further difficulty in the evaluation of a series of this type is in the selection of a group of theoretically normovolemic patients. It has been recognized for many years that changes in blood volume occur with increasing age, and a wide variance from the normal may result from chronic illness. The difficulties in selecting normal patients is increased by the presence of obesity, since there is a good correlation between blood volume and lean body weight but this correlation is not constant with increasing degrees of obesity.

In the initial part of this report, a comparison of the blood volume in groups of hypertensive and normotensive patients is made. In the second part, the blood volume changes associated with the surgical therapy of essential hypertension by bilateral, staged adrenalectomy and a modified Adson type of subdiaphragmatic sympathectomy are presented.

METHODS

With chromium 51 (Cr^{51}) labelled erythrocytes the total body hemoglobin mass was measured and the blood volume calculated in a group of patients with severe hypertension and in a group of normotensive patients. The selection of normal patients as controls for comparison with the hypertensive patients was made by studying a large group of individuals who were similar to the hypertensive group with regard to age, height, weight, and sex and who showed no evidence of hypertension or chronic disease.

From the Harrison Department of Surgical Research, and the Edward B. Robinette Foundation of the Hospital and Schools of Medicine of the University of Pennsylvania, Philadelphia.

TABLE I.—NORMOTENSIVE FEMALE PATIENTS

Patient	*Age, yrs.*	*Height, inches*	*Weight, kilos*	*Hemoglobin, gm./100 ml.*	*Blood volume, ml./kilo*
1	62	67	54.6	13.0	73.7
2	52	61	52.3	13.9	63.6
3	60	63	51.8	13.3	70.4
4	48	62	49.5	13.0	71.4
5	51	64	72.1	12.4	75.3
6	45	61	39.3	13.3	81.2
7	42	62	60.7	16.7	71.4
8	49	68	59.1	12.8	65.4
9	35	64	60.9	13.5	60.2
10	29	62	49.2	13.1	70.2
11	57	62	51.1	13.9	68.7
12	37	62	56.8	12.8	73.7
13	40	62	52.3	13.2	73.4
14	49	60	51.4	13.5	63.0
15	48	67	82.7	13.0	68.3
16	46	65	64.5	12.3	72.4
17	44	65	71.4	12.9	69.9
18	48	63	64.4	12.5	65.2
19	45	64	51.1	13.4	72.4
	46.7	63.4	57.6	13.3±0.5	70.0±3.88

A specific rather than a random selection of the group of normal patients was made in an attempt to eliminate variables other than the presence or absence of hypertension. It is recognized that random sampling might have given a more desirable control group, if it had been possible to eliminate all other variables that could produce changes in blood volume. This, however, was not possible, and a statistical evaluation would have been meaningless unless the specific selection had been accomplished. No patient was included in the series if the peripheral circulating hemoglobin concentration was less than 12.5 grams per cent. Patients were also excluded because of any chronic systemic disease, congestive heart failure, or history of blood loss from any cause.

A selected group of hypertensive patients was subjected to operative therapy for this disease. Additional blood volume determinations were performed 72 to 96 hours after the first operation, before and 72 to 96 hours after the second operative procedure, and at intervals of 2 to 36 months after the operation.

The technique of labelling the erythrocytes with radioactive chromium consists of:

1. Five milliliters of ACD solution are added to a vacuum bottle.

2. Fifty milliliters of the patient's blood are transferred into the bottle.

3. Seventy-five microcuries of sodium chromate (Cr-51) are added.

4. The red cells are then incubated at 6 degrees C. for 1 hour, and then centrifuged at 6 degrees C. for 30 minutes at 1,500 revolutions per minute.

5. The supernatant is decanted.

6. One hundred fifty milliliters of cold sterile saline are added as a wash and steps 4 and 5 are repeated.

7. The decanted supernatant is replaced to approximately the original volume with 0.9 per cent saline cooled to 6 degrees C.

8. After thorough mixing, 5 milliliters of the final suspension are removed for use as a reference standard (S).

9. If the patient had a previous blood volume determination using radioactive materials, a preinjection sample of blood is obtained and the radioactivity measured as a blank (B). Thirty milliliters are then injected intravenously into the patient.

10. Samples (X) are drawn after 15, 30, and 60 minutes.

11. The concentration of radioactivity of all samples, the blank and the standard, is determined in counts per minute in a well-type scintillation counter by counting hemolyzed aliquots.

12. The hemoglobin concentration of the samples, blank and standard, is determined by conversion to cyanmethemoglobin and measuring in a Beckman Model B spectrophotometer at 540 millimicra.

13. A hematocrit of the samples is determined by a microhematocrit technique. The hematocrit of the samples is then corrected for plasma trapped in the interstices between red cells (3 per cent) and for the relation of peripheral to total body hematocrit (90 per cent).

The calculations are as follows:

1. Concentration of the radioactivity in the standard (S), blank (B), and samples (X) is determined in counts per minute per gram of hemoglobin.

$$\text{The dilution} = \frac{\text{counts/min./gm. Hb. (S)}}{\text{counts/min./gm. Hb. (X)-counts/min./gm. Hb. (B)}}$$

2. Total hemoglobin injected = Hb. conc. (gm./100 ml.) (S) × ml. (S) injected.

3. Total body hemoglobin = dilution factor × total hemoglobin injected.

4. Red cell volume =

$$\frac{\text{total body hemoglobin} \times \text{hematocrit} \times 0.97}{\text{circulating hemoglobin concentration of X}}$$

5. Blood volume = $\dfrac{\text{red cell volume}}{\text{hematocrit} \times 0.87}$

Hemoglobin loss at the time of operation and during the immediate postoperative

period was determined by comparing the total body hemoglobin preoperatively with the postoperative determination. Since the volume of blood transfused was known, hemoglobin loss then equaled the sum of the preoperative total hemoglobin and the total hemoglobin transfused minus postoperative total body hemoglobin. Each bottle of transfused blood was assumed to contain 67.2 grams of hemoglobin. This approximate figure was determined by using an average donor circulating hemoglobin concentration of 14.0 grams per cent. When 480 milliliters of this blood are added to 120 milliliters of citrate, the hemoglobin concentration then becomes 11.2 grams per cent, and the administration of 600 milliliters of blood with the hemoglobin concentration is the equivalent of that of 67.2 grams of hemoglobin per bottle of blood. An approximation of the volume of blood lost can be determined by:

$$\frac{\text{Total hemoglobin loss (gms.)}}{\text{Postoperative peripheral hemoglobin concentration (gm./100 ml.)}}$$

The hemoglobin concentration of the blood lost will vary, and no correction has been made for this factor. An approximation of the average value can be made by utilizing the postoperative peripheral hemoglobin concentration in the calculations. Measured blood loss at the time of operation was obtained by the addition of blood loss calculated by weighing sponges, measuring the amount in suction bottles, and estimating the blood lost on the surgical drapes.

RESULTS

Data from a group of 16 hypertensive and 19 normotensive female patients were compiled. Table I shows the tabulated data from the 19 normotensive female patients. The average age of this group was 46.7 years; the average height was 63.4 inches; the average weight was 57.6 kilograms, and the mean circulating hemoglobin concentration was 13.3±0.5 grams per cent. In Table II are the findings from 16 hypertensive females with an average age of 46.9 years, an average height of 63.2 inches, an average weight of 62.6 kilograms, and a mean peripheral circulating hemoglobin concentration of 13.8±0.8 grams per cent.

TABLE II.—HYPERTENSIVE FEMALE PATIENTS

Patient	*Age, yrs.*	*Height, inches*	*Weight, kilos*	*Hemoglobin, gm./100 ml.*	*Blood volume, ml./kilo*
1	56	59	58.6	13.1	63.9
2	43	67	63.6	14.1	69.4
3	32	64	54.5	13.5	65.7
4	31	63	58.6	12.5	57.6
5	51	63	59.5	13.8	71.4
6	50	62	51.6	14.0	57.5
7	60	64	64.5	16.3	63.9
8	50	65	57.7	16.6	58.1
9	39	62	51.8	14.3	65.7
10	44	67	80.0	14.1	48.5
11	45	65	66.8	13.7	61.9
12	51	62	57.4	14.6	68.1
13	51	59	77.7	13.1	53.5
14	55	63	69.5	15.8	58.2
15	43	64	67.3	13.5	59.2
16	50	62	62.4	13.9	52.9
	46.9	63.2	62.6	13.8±0.8	61.0±5.28

TABLE III.—NORMOTENSIVE MALE PATIENTS

Patient	*Age, yrs.*	*Height, inches*	*Weight, kilos*	*Hemoglobin, gm./100 ml.*	*Blood volume, ml./kilo*
1	62	67	64.6	13.2	73.7
2	38	68	71.4	14.0	78.7
3	55	66	67.4	13.1	89.9
4	61	63	76.4	13.9	80.8
5	50	68	75.0	17.1	80.2
6	46	69	66.4	15.2	70.4
7	35	71	68.5	16.8	73.6
8	29	71	68.9	14.5	83.0
9	51	65	58.8	14.3	71.4
10	55	72	78.6	13.2	78.5
11	62	72	83.2	14.1	83.0
12	42	69	68.2	12.6	71.9
13	47	72	77.3	14.2	81.0
14	60	68	58.3	13.4	70.4
15	50	65	72.3	15.1	73.0
16	26	71	66.3	15.1	75.1
17	28	72	78.8	14.6	76.5
18	26	70	68.2	15.3	73.0
19	48	69	67.3	13.0	71.4
20	38	68	65.4	14.2	76.3
21	62	62	61.4	18.2	73.7
22	32	71	70.0	13.2	78.9
23	45	71	86.4	15.3	70.6
24	44	67	76.4	17.2	66.0
25	31	64	64.1	13.7	80.4
26	44	75	81.8	17.8	75.8
	43.8	68.7	70.8	14.3±1.2	76.1±4.17

In Table III the data from 26 normal males are tabulated. The average age was 43.8 years, the average height 68.7 inches, the average weight 70.8 kilograms, and the mean peripheral circulating hemoglobin concentration 14.3±1.2 grams per cent.

In Table IV data from 21 hypertensive

TABLE IV.—HYPERTENSIVE MALE PATIENTS

Patient	*Age, yrs.*	*Height, inches*	*Weight, kilos*	*Hemoglobin, gm./100 ml.*	*Blood volume, ml./kilo*
1	55	72	75.5	16.4	60.9
2	45	70	78.3	13.9	58.5
3	51	62	69.6	15.4	64.5
4	51	68	86.4	13.2	66.7
5	37	69	67.8	13.0	58.9
6	54	68	64.8	13.9	65.6
7	34	73	87.7	12.8	65.6
8	52	69	65.2	13.0	62.7
9	47	66	73.2	12.9	63.3
10	39	69	71.8	15.2	74.4
11	50	66	81.8	13.9	72.4
12	39	67	62.3	15.3	74.7
13	43	71	59.1	14.7	69.1
14	49	66	89.5	17.8	64.9
15	47	70	63.6	13.2	70.7
16	41	66	70.5	14.7	66.1
17	44	67	75.5	15.5	66.3
18	50	66	59.1	14.6	79.6
19	47	65	63.6	14.4	78.8
20	35	71	80.5	14.6	69.7
21	45	64	77.3	13.3	63.7
	45.4	67.8	72.6	14.4±1.0	67.5±5.92

male patients are tabulated. The average age is 45.4 years, the average height 67.8 inches, the average weight 72.6 kilograms, and the mean peripheral circulating hemoglobin concentration 14.4±1.0 grams per cent.

The normal patients in the female group had a mean blood volume of 70.0±3.88 milliliters per kilogram of total body weight, while those in the hypertensive group had a mean blood volume of 61.0±5.28 milliliters per kilogram of total body weight. These figures were shown to be statistically significant with a "T" value of 5.66.

The normal patients in the male group had a mean blood volume of 76.1±4.17 milliliters per kilogram of total body weight, while the hypertensive patients in the male group were found to have a mean blood volume of 67.5±5.92 milliliters per kilogram of total body weight. These figures were also found to be statistically significant when subjected to analysis showing a "T" value of 5.62.

These figures indicate that the average normotensive male or female has a blood volume normally of about 500 to 700 milliliters greater than the average hypertensive patient of similar physical characteristics, sex, and age.

A carefully selected group of these hypertensive patients was found to be refractory to medical therapy of this disease and accordingly were considered candidates for surgical treatment. The operative procedure consisted of a bilateral total or subtotal (95 per cent) adrenalectomy and an Adson type of sympathectomy performed in 2 stages with a varying time period between the staged procedures. The patients were operated upon by a total of 6 surgeons; 2 were staff members and 4 were residents. Meticulous care was taken to insure hemostasis, and at the time of closure of the incision no evidence of hemorrhage was present.

The postoperative course of many of these patients after adrenalectomy and sympathectomy was complicated by hypotension which required the transfusion of large volumes of blood for the maintenance of acceptable levels of blood pressure, i.e., systolic pressure greater than 130 millimeters of mercury. The administration of pressor substances usually provided only temporary relief of the hypotension.

It was noted that transfusions of whole blood were generally required to maintain the blood pressure. The volumes of blood required for transfusion in the first 72 to 96 hours after the beginning of the operation were considerably greater than the weighed blood loss at the time of operation. Several possibilities other than technical failure were suggested as to the nature of this complication. The first was that sequestration of blood or red cells in a dilated splanchnic bed had occurred and that the hypotension was secondary to this relative hypovolemia. The second was that the hypotension was secondary to adrenal insufficiency, while the third was the development of postoperative retroperitoneal hemorrhage.

Table V is a tabulation of the quantity of blood lost at the staged operative procedures with a comparison of the measured and estimated blood loss found at the time of the same operative procedure. In 23 of the 49 operations performed the blood loss during operation and the immediate postoperative

TABLE V.—QUANTITY OF BLOOD LOST AT OPERATION

Patient		1st stage			2nd stage			
Age, yrs.	*Sex*	*Blood loss, gm. Hb.*	*Blood loss, ml.*	*Blood loss, measured*	*Blood loss, gm. Hb.*	*Blood loss, ml.*	*Blood loss, measured*	*Evidence of retroperitoneal hemorrhage*
35	M	260	1932	660	188	1396	600	
55	F	175	1301	350				
50	M	138	1028	400	217	1610	430	Drainage hematoma
51	F	93	690	600	94	696	200	
44	M	261	1939	300	62	460	400	Drainage hematoma
41	M	143	1060	650	314	2333	900	Drainage hematoma
54	F	182	1356	580	337	2504	700	Died of CVA postop; autopsy showed retroperitoneal hematoma
49	M	228	1699	450	1174	8731	560	Drainage hematoma
42	M	317	2358	300	206	1533	250	Drainage hematoma
32	F	285	2123	960	167	1240	800	Drainage hematoma
39	M	721	5368	1000	176	1306	397	Drainage hematoma; palpable abd. mass
39	M	372	2771	1100	106	789	500	
50	M	465	3458	1100	87	643	517	
44	F	187	1394	700	351	2609	280	Drainage hematoma
53	F	233	1731	200	305	2269	350	Drainage hematoma
31	F	138	1018	470	386	2870	780	Drainage hematoma
42	M	393	2923	600	833	6198	800	Drainage hematoma; palpable abd. mass
32	F	104	775	400	266	1976	300	
56	F	61	450	250	278	2071	200	
42	M	545	4057	2000	1486	11060	1000	Re-explored, bleeding; retroperitoneal hematoma
54	F	109	813	610				
34	M	243	1809	350				
50	F	899	6656	818				Drainage hematoma
48	F	350	2603	1000				Died myocardial infarct. postop.; autopsy, retroperitoneal hematoma
43	F	172	1278	680				Drainage hematoma
45	M	312	2318	1450				
47	M				123	914	800	
45	F				303	2251	800	Drainage hematoma
39	F				94	697	300	
47	M				255	1900	420	Drainage hematoma

The first or second stage blood loss (gm. Hb.) is the calculated value based on the total body hemoglobin measurements and the first or second stage blood loss (ml.) is the value calculated from the (gm. Hb.) value. The measured value (ml.) is the value calculated from weighing sponges and drapes in the operating room. Clinical evidence for retroperitoneal hematoma accumulation is presented in the last column.

period was 1,900 milliliters or greater, and in 6 of these 49 cases the blood loss as measured by the Cr^{51} tagged erythrocyte technique was greater than 4,000 milliliters of blood.

The possibility that this loss of blood from the circulation was due to sequestration in postsympathectomy atonic vascular beds was considered. Figure 1 shows the total body hemoglobin determinations on 1 patient who had serial determinations of total hemoglobin values made for several days after the operative procedure. This demonstrates that no "autotransfusion" occurred during the immediate postoperative period. An increase in total hemoglobin would have indicated that tagged erythrocytes which had previously been sequestered in dilated vascular beds had re-entered the general circulation and had resulted in an increase in the total hemoglobin mass measured. The same studies were made in 3 other patients and similar data were found.

The extent of this blood loss can be appreciated in Figure 2, where the calculated operative blood loss in the immediate postoperative period is plotted as the percentage of the preoperative total body hemoglobin. After operation 32 patients lost greater than 30 per cent of the preoperative total body hemoglobin and after 17 procedures, a loss greater than 50 per cent of the total body hemoglobin was found. This series includes 6 patients in whom only a first stage procedure was performed. The 4 patients in whom only the figures for the second stage

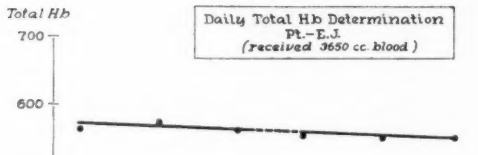

FIG. 1.

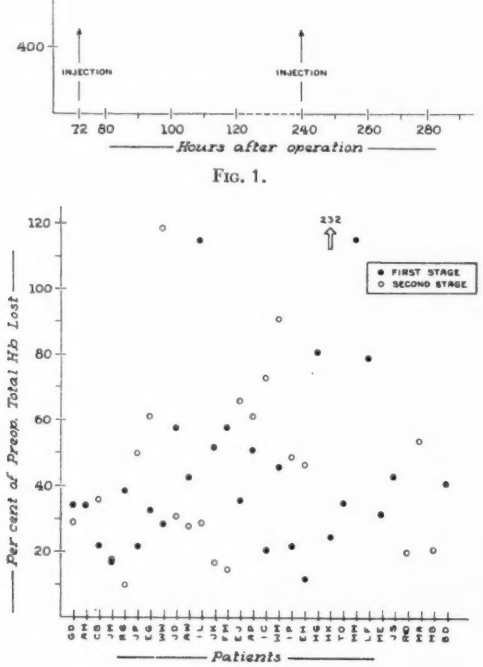

FIG. 2.

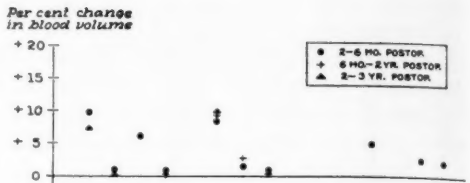

FIG. 3.

FIG. 1. Daily total body hemoglobin calculations indicate that autotransfusion from sequestered blood did not occur and that the hemoglobin loss from the circulation was a loss into the extravascular space rather than an apparent loss into a dilated vascular bed.

FIG. 2. The total body hemoglobin loss based on a percentage of the total body hemoglobin present prior to the operative procedures. The first stage procedures are the solid circles while the second stage procedures are the clear circles.

FIG. 3. Graphic representation of repeated blood volume determinations in hypertensive patients who had undergone surgical therapy. The stability of the blood volume regardless of the response to therapy suggests no correlation between a response to therapy and a return to a normovolemic state. The stability of the determination also suggests a homeostatic mechanism which maintains blood volume at a relatively stable level over long periods of time.

are available are those in whom the first stage of the operation was performed prior to the onset of the study.

After operation the blood volume determinations of these patients were repeated at time intervals of 2 to 36 months. No follow-up studies were made on patients who had not had complete volume studies at the time of the operative procedures.

Figure 3 graphically represents the blood volume changes that were noted in these patients during the follow-up period. The greatest change of blood volume was noted in patient V.H., when the postoperative blood volume change was +9.8 per cent. In only 2 patients (V.H. and E.J.) were the blood volume changes greater than ±6.2 per cent and in the remainder of the patients the change was less than ±5 per cent.

DISCUSSION

The smaller blood volumes in hypertensive patients are in keeping with the vasospasm which occurs with the disease. This vasospasm which at first may be neurogenic may later be superseded by a permanent increase in the peripheral resistance. While this concept has been accepted as applied to the arterial circulation, it has never been shown to exist in the venous bed, and venous

constriction or changes in the lesser circulation may be greater factors in producing the changes in blood volume observed in the patients in this report. The data are statistically significant and indicate that a real variance between the mean volumes of normal and hypertensive patients does exist. True random selection of normotensive individuals was not made, but the group was selected to be similar to the hypertensive group in those factors which are presently known to affect blood volume.

The apparent excessive loss of blood after the operative procedure for correction of hypertension may be caused by a number of factors which are not yet determined. Among these may be: (1) changes in the production of physiologically active adrenal medullary or cortical substances; (2) arteriosclerotic changes commonly found in the blood vessels of hypertensive individuals which may allow for less efficient constriction of small vessels in the operative area; (3) the effect of excising the sympathetic nerves; (4) a large potential dead space produced by retroperitoneal exploration which may be further effected by diaphragmatic movement and pressure changes associated with respiratory effort.

The data of the repeated blood volume determinations over 2 months to 3 years after operation could not be correlated with any clinical results of the operative procedure with regard to amelioration of the hypertension or restoration of normal blood pressures. This observation suggests that the blood volume is not affected by the operative procedure, at least while the patients are maintained on daily replacement therapy of cortisone (25 to 37.5 mgm.), desoxycorticosterone acetate or 9-alpha-fluorohydrocortisone (0.05 mgm.), and sodium chloride (2 gm. in summer). The weight of many of these patients changed slightly during the time interval of the study but the data are presented in terms of milliliters per kilogram of body weight, and the blood volume expressed in this parameter did not change significantly. This fact suggests the possibility that, while the blood volume of any like group of individuals may vary widely from the mean of that group, the total blood volume of an individual is stable for relatively long periods of time and is more directly dependent upon weight than on other factors. Factors other than blood pressure changes (adrenalectomy with selected steroid replacement, limited sympathectomy) maintain blood volume despite lowering of the blood pressure.

SUMMARY

1. A statistically significant difference has been demonstrated between the blood volume of normotensive and hypertensive patients—70.0 ± 3.88 milliliters per kilogram for females; 76.1 ± 4.17 milliliters per kilogram for males: 61.0 ± 5.28 milliliters per kilogram for females; 67.5 ± 5.92 milliliters per kilogram for males, respectively.

2. The hypotension during the immediate postoperative period following total adrenalectomy and Adson modified sympathectomy may be restored to acceptable levels of blood pressure (130 millimeters mercury systolic) by the administration of larger quantities of blood than can be measured and estimated to be lost at the time of the operative procedure, and is partly due to retroperitoneal hemorrhage.

3. The blood volumes of the patients subjected to bilateral total adrenalectomy and Adson sympathectomy were observed for a period of 2 months to 3 years after operation. The volumes were found to vary only within the limits of laboratory error in all but 2 patients. The blood volume changes of the remainder were found to be within 5 per cent of the original blood volume determination in terms of milliliters per kilogram of body weight. No correlation could be found between blood volumes and clinical response to the operation in terms of restoration to the normal blood pressure.

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THE USE OF THE WOOKEY OPERATION FOR CARCINOMA OF THE HYPOPHARYNX AND CERVICAL ESOPHAGUS

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In 1942, Wookey described a surgical technique which he had developed for dealing with carcinoma of the lower part of the pharynx and upper portion of the esophagus. This operation is a two stage procedure described and illustrated in a previous article (6). At the first operation a transversely placed rectangular full thickness skin flap is fashioned. The involved tissue is then excised, usually the larynx, pharynx, and upper cervical esophagus (Fig. 1a), less commonly the cervical esophagus only. The flap is then utilized to construct a deep skin-lined groove connecting the pharynx above and the esophagus below. A period of 6 to 12 weeks is then required for the transplanted skin to pick up an adequate blood supply from its new bed (Fig. 1b).

At the second operation the groove is converted into a skin tube by making a circumferential incision about it and allowing its margins to be turned in and sutured together. Direct closure of the resulting skin defect has, in my experience, almost always been possible (Fig. 1c). Swallowing is allowed as soon as healing has occurred, and a full diet can soon be easily managed. In most cases the cosmetic result is remarkably good (Fig. 2).

The patient in Wookey's first case of this type was operated on 19 December 1934. She had an excellent result, lived and ate for 2 years, then died of cervical metastases. From that time until the end of 1959 in the Toronto General Hospital a further 43 patients have undergone this operation (Table I), 30 by Wookey and 14 by the author. All but 1 patient (Case 3) had squamous cell carcinoma involving the hypopharynx[1] or cervical esophagus and causing severe dysphagia. This surgical procedure was the primary treatment in 38 of the whole group; 6 were operated upon for residual or recurrent disease after an attempt at cure by radiation therapy.

The age distribution of these patients is shown in Table II. There were 13 male patients and 31 females in this group. Of 381 patients with carcinoma of the esophagus studied, it is remarkable that the hypopharynx is the only area between lips and stomach in which carcinoma is more common in women than in men (7). This anomalous sex incidence may be partly accounted for by the Paterson-Kelly (Plummer-Vinson) syndrome which, occurring only in females, is characterized by hypochromic anemia, smooth tongue, upper esophageal dysphagia, spoon-shaped nails, gastric anacidity, and sometimes other stigmas. Ahlbom has shown a definite correlation between this syndrome and the occurrence of carcinoma of the mouth, pharynx, and esophagus. Negus has described a chronic hypopharyngitis in these patients which he believes to be a common precursor of carcinoma in that area. Indeed, when the premalignant change does not promptly respond to simple measures, he advocates excision of the involved segment of the gullet. The evidence on this point is, however, far from complete; many women with carcinoma of the hypopharynx cannot be shown to have the Plummer-Vinson syndrome, while only a very

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[1]Hypopharynx: that part of the laryngopharynx below the upper border of the cricoid cartilage.

TABLE I.—OPERATIONS PERFORMED BY THE WOOKEY TECHNIQUE, TORONTO GENERAL HOSPITAL, 1934 TO 1960

Periods covered	*No. of patients*
1934 to 1938	2
1939 to 1943	6
1944 to 1948	13
1949 to 1953	13
1954 to 1958	8
1959	2
Total	44

TABLE II.—AGE DISTRIBUTION OF PATIENTS

Age, years	*No. of patients*
30 to 39	1
40 to 49	5
50 to 59	22
60 to 69	13
70 Plus	3
Total	44

Males 13; females, 31.

TABLE III.—RESULTS IN PATIENTS TREATED BY THE WOOKEY OPERATION

Tissue excised	*No. of operations*	*Op. deaths*	*Living after operation* — *1 year*	*3 years*	*5 years*
Cervical esophagus only.	15	1	8	5	3
Larynx and pharyngoesophagus	29	5	15	7	6
Totals No.	44	6	23	12	9
Per cent		14		30	24

few with the syndrome ever have cancer. Among our own series the information is inadequate to support any opinion. The history of our most recent case of hypopharyngeal carcinoma is, in this context, of great interest:

A 33 year old woman was married at the age of 20 years and now has 5 children between the ages of 2 and 12 years. She believes that she has been anemic for many years. About 11 years ago she first noticed spooning of her fingernails and a diagnosis of anemia was made. Iron pills were prescribed but she took them for only about 1 month. She had her menarche at the age of 13 years; since then her menstrual periods have been characterized by a very heavy flow lasting about 1 week.

For many years she has had some difficulty in swallowing certain solid foods such as apples and salads which would seem to stick at the base of her throat. During the past 2 years she has had repeated "sore throats," tonsillitis, and two bouts of "quinsy." Since November 1958 she has had more marked difficulty in swallowing.

Tonsillectomy was performed 8 June 1959. After that the dysphagia became much more marked and she began to lose weight quickly. During August 1959 her voice became very weak and since then she has been able to speak only in a whisper.

She was recently examined in a hospital in northern Ontario, found to have carcinoma of the hypopharynx, and referred to the Toronto General Hospital where she was admitted 22 November 1959.

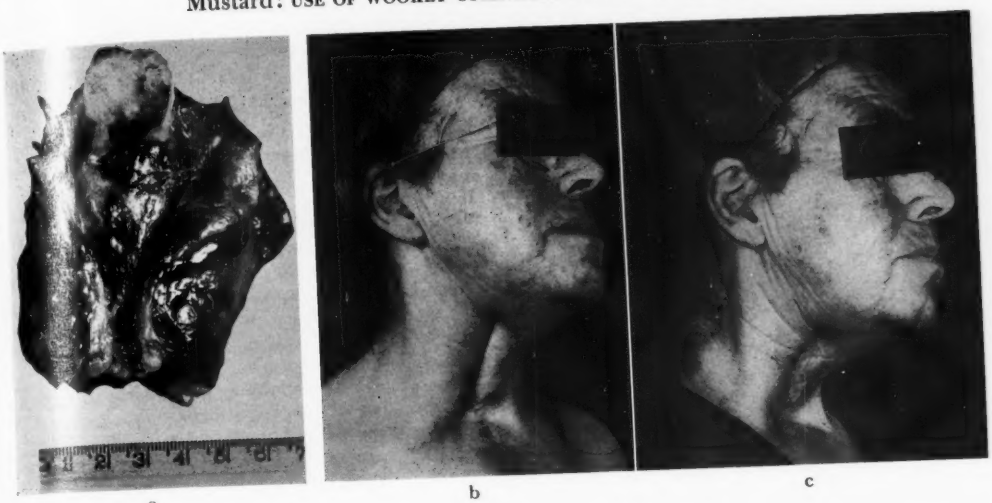
At this time her weight was 92 pounds; 1 year ago she weighed 118 pounds. She was able to swallow only small amounts of liquid. Her tongue appeared normal. The right vocal cord was fixed. There were several palpable lymph nodes in the upper right side of the neck. The larynx and thyroid seemed widened on the right side. Her fingernails were markedly spoon-shaped. Apart from emaciation the remainder of the physical examination was negative.

The patient's hemoglobin was 60 per cent of normal; the blood smear showed marked hypochromasia, microcytosis, and anisocytosis. Unfortunately she was given several blood transfusions before more complete blood studies were made.

Direct laryngoscopy and bronchoscopy demonstrated a large ulcer involving the whole hypopharynx and extending up into the right pyriform fossa and along the posterior wall of the oropharynx. The trachea did not appear to be invaded but it was compressed in the subglottic area. Biopsies from the ulcer were reported as anaplastic carcinoma.

It is considered that this young woman has had chronic iron-deficiency anemia for many years, due to excessive blood loss at menstrual periods plus the loss to the fetus during each of her 5 pregnancies, without adequate replacement in her diet or by medication. It certainly seems reasonable to suppose that the changes in the hypopharynx which caused her mild dysphagia for many years were also responsible for the development there of carcinoma at an unusually early age. It is interesting to speculate that adequate iron therapy during the past 10 years might have prevented the malignant change which now threatens her life.

The results in this series of 44 patients treated by the Wookey operation are shown in Table III. It is seen that in 29 the larynx and pharyngoesophagus were excised, while in 15 cases the larynx was spared. There were 6 operative deaths (14 per cent) all after the first stage procedure. Just over one-half of the group survived for 1 year after operation. Twelve (30 per cent) were living at 3 years after operation. So far there have been 9 five year survivors, i.e., 24 per cent of those operated upon up to January 1955, a salvage rate for the procedure which, contrasted with the utterly hopeless outlook of



a b c

FIG. 1.

a b

FIG. 2.

FIG. 1. a, Surgical specimen opened in midline posteriorly to show extensive tumor of hypopharynx spreading up onto back of larynx. b, Just prior to second stage operation; note deep skin-lined groove connecting pharynx and esophagus. c, Reconstruction completed, swallowing normal.

FIG. 2. Two good cosmetic and functional results after completed Wookey procedures.

TABLE IV.—LONG SURVIVORS OF THE WOOKEY OPERATION

Case No. *Sex*	*Date of first procedure*	*Living since operation*
1 M	Feb. 1948	12 yrs.
2 F	Apr. 1948	11 yrs.*
3 M	Dec. 1948	4 yrs. 10 mos.* Died, extraneous disease
4 F	Mar. 1949	10 yrs. 10 mos.
5 F	July 1949	10 yrs 4 mos.
6 M	Jan. 1951	5 yrs. 4 mos.* Died, extraneous disease
7 M	Nov. 1952	6 yrs.* 10 mos. (R)
8 F	Jan. 1953	5 yrs. (then lost)
9 M	Mar. 1954	5 yrs. 10 mos.
10 F	Feb. 1955	5 yrs.
11 F	Jan. 1956	4 yrs.(R)

*Larynx spared.
(R) Postop. radiation.

the untreated disease, seems to justify a sincere tribute to the ingenuity and courage of the originator of the operation.

In addition to these 9 five year survivals there have been 2 other patients with gratifyingly long survival. These 11 patients (Table IV) are rich dividends for the effort and anxiety involved. Their histories are summarized below. It will be noted that in 4 of these patients it was not necessary to remove the larynx. Two of the group, Cases 9 and 11, were operated on after the failure of intensive radiation therapy to control their disease. None of the others had any preoperative radiation. Only 2, Cases 7 and 11, have been given irradiation postoperatively for recurrent disease; 3 other male patients, Cases 1, 3, and 6, were given superficial irradiation between the first and second stage operations in an attempt to produce epilation of the skin which would line the reconstructed esophagus. In all others, the disease has been controlled solely by excision. Ten of the 11 long survivors have been able to eat normal meals with little difficulty; only 1, Case 8, has had multiple fistulas due to previous radiation plus operation, requiring repeated plastic operations over a period of 2½ years before closure was finally accomplished.

Case 1. This 51 year old farmer was admitted 27 January 1948. Two months before, after an acute upper respiratory infection, this previously healthy man began to notice difficulty in swallowing. Since that time, he had had some pain on swallowing referred to the right ear and he had occasionally spit up small amounts of bloody mucus. He thought his throat had been "small" for years. General physical examination was negative. Hemoglobin level was 92 per cent and red cell count was 4,600,000. Laryngoscopic examination showed an ulcerating mass behind the larynx and in the right pyriform sinus. Vocal cords moved normally. Biopsy was reported as squamous cell carcinoma.

On 11 February 1948 laryngopharyngectomy was carried out with first stage skin tube reconstruction of the esophagus. The left lobe of the thyroid was preserved. The pathologic examination confirmed the diagnosis of squamous cancer; lymph nodes with the specimen did not contain metastatic tumor. After healing was complete the patient was referred to the Department of Radiotherapy for epilation of the skin which would form the new esophagus. Eighty-eight kilovolt therapy to a total dosage of 3,000 roentgens was applied to the right anterior part of the neck during the period 24 March to 19 April.

This man remains perfectly well up to January 1960 (Fig. 3). He successfully underwent a transurethral resection of his prostate in May 1959; chest roentgenogram at that time was negative. He has continued to work his farm and has been able without difficulty to eat enough to maintain weight and strength. He has learned an imperfect form of pharyngeal speech, poor but understandable. His survival to date since operation is 12 years.

In January 1951 he complained of hair regurgitating into his mouth occasionally, and extensive hair growth in the skin tube was demonstrated by roentgenographic studies. In April 1952 he again had similar complaints. However, in February 1955 he no longer had any difficulty about hair, and examination failed to demonstrate hair growth in the tube at that time.

Case 2. This 61 year old woman was admitted 10 March 1948. She had had increasing dysphagia for 2½ months. Barium swallow roentgenogram and esophagoscopic examination showed an ulcerating constricting lesion beginning in the retrocricoid area and extending 1½ inches down into the cervical esophagus. Biopsy indicated the diagnosis of squamous cell carcinoma. She also had a very large nodular

goiter. Her hemoglobin was 86 per cent and the red cell count was 4,600,000.

On 19 April 1948 the hypopharynx and cervical esophagus were excised; the larynx was spared. The right hemithyroid with a portion of the left lobe of the thyroid was also removed. The pathologic report confirmed the biopsy diagnosis; no lymph nodes were described in the specimen. The second stage operation was successfully performed 10 July 1948. No radiation therapy has been given at any time.

This patient last reported 17 April 1959, at which time she was perfectly well, able to eat and talk without difficulty, and to carry out all normal activities. Her survival time since operation is 11 years.

CASE 3. This 64 year old man was admitted 13 December 1948. He had had a duodenal ulcer for many years, first shown by roentgenogram in 1924, and causing three hemorrhages up to 1936. In June 1948 he began to notice increasing difficulty in swallowing solid food. Esophagoscopic examination on the day after admission to the hospital showed a firm but ulcerating mass almost completely filling the lumen of the esophagus 3 centimeters below the cricopharyngeus muscle. The lower level of the lesion could not be ascertained. A biopsy was reported to show adenoma.

Cervical esophagectomy with preservation of the larynx was performed on 20 December 1948. The pathologist described in the center of the excised esophagus a roughened area of mucosa 0.8 centimeter in diameter, deep to which there was some thickening of the esophageal wall. On microscopic study this esophagus presented a most unusual picture. In the midst of the stratified squamous epithelium lining the mucosa there was an area of columnar epithelium. This had the appearance of gastric mucosa, with crypts extending half way down to the muscularis mucosa, the rest of this layer being composed of glands. Some of these glands appeared to have undergone malignant degeneration, to have invaded the submucosa widely, and to have extended for a considerable distance into the muscularis externa. The pathologic diagnosis was adenocarcinoma of the upper end of the esophagus.

In order to produce epilation in the skin tube, surface radium to a dosage of 70 milligram hours was applied to the skin of the right side of the neck 21 January 1949. Between 7 and 24 February 1949, 88 kilovolt radiation therapy was given to the same area to a dosage of 1,500 roentgens. The second operation was carried out 8 March 1949, producing an excellent skin tube replacement of the cervical esophagus through which the patient could eat normally. In January 1951 he returned complaining of hair regurgitating into his mouth. Further radiation treatment was given 1 to 6 February 1951, using the 400 kilovolt machine to a total dose of 1,500 roentgens.

On 23 October 1953 this man died of a heart attack, 58 months after his first operation. At no time was there evidence of recurrence of his malignant disease.

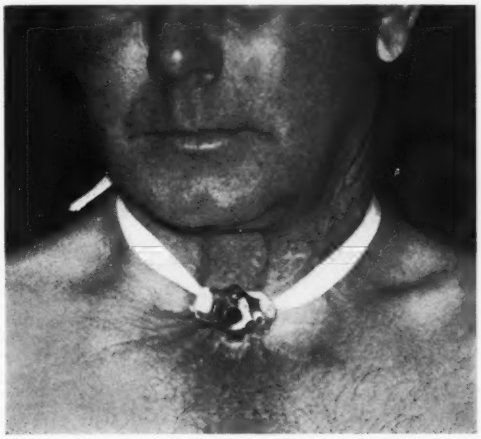


FIG. 3. Case 1. Appearance of patient in January 1953. Laryngopharyngectomy and skin tube reconstruction were performed in February and in April 1948.

CASE 4. This 54 year old woman was admitted 27 February 1949. She was found to have a squamous cell carcinoma extending from the retrocricoid area down into the cervical esophagus. Her hemoglobin level was 78 per cent and the red cell count was 3,800,000; the red cells showed slight variation in size and slight polychromasia.

The larynx, lower part of the pharynx, and the cervical esophagus were excised 2 March 1949. A portion of the left lobe of the thyroid was preserved. The tumor mass was found to be about 6 centimeters long and to be invading forward into the trachea at a point 1.0 centimeter below the cricoid. The lymph nodes examined with the specimen were free of metastatic disease. Construction of the skin tube esophagus was completed at the second operation, 2 May 1949.

This patient has remained perfectly well since that time up to July 1959, a period of 10 years, 10 months (Fig. 4). No radiotherapy has been given at any time. She eats normally, has gained weight, and does all her own housework. She talks very clearly by means of an electric vibrator which she holds against her neck to produce a sound which is modified into speech by tongue, palate, and lips, in the usual way.

CASE 5. This 48 year old woman was admitted 27 June 1949. For 6 months she had noticed "sticking" in her throat on swallowing. During the past 6 weeks dysphagia had become much worse; she had lost 15 pounds in weight. Her hemoglobin level on admission was 85 per cent. Direct examination showed an irregular mass in the right pyriform sinus extending down to involve the postcricoid area. Biopsy was reported as squamous cell carcinoma.

Laryngopharyngectomy was carried out 4 July

a b

FIG. 4. Case 4. Appearance of patient in April 1955. Laryngopharyngectomy was performed in May 1949. a, Good cosmetic result. b, Electric buzzer held against side of neck to give "voice."

1949. Lymph nodes attached to the specimen were all free of tumor. The second stage operation was performed 11 October 1949. No radiation therapy has been given.

This patient was perfectly well and able to eat normally when seen 27 November 1959 (Fig. 5). Her survival since operation is 10 years 4 months.

CASE 6. This 58 year old man was admitted 6 January 1951. He had had progressive dysphagia only since December 1950. Examination showed an ulcerating tumor on the posterior wall of the hypopharynx, biopsy of which showed squamous cell carcinoma.

Cervical esophagectomy was carried out on 15 January 1951. The tumor was found to be about 3 to 5 centimeters long, lying on the posterior wall of the hypopharynx and upper cervical esophagus. It was easily excised with a generous margin; the larynx was spared. The original diagnosis was confirmed by pathologic examination; lymph nodes in the specimen contained no tumor.

Depilation therapy was given as follows: 9 February 1951, 50 milligram hours of surface mould radium to the neck; 23 February to 4 March 1951, 1,850 roentgens of 88 kilovolt radiation to the neck; and 9 March 1951, 42.5 milligram hours radium mould to the neck. At the second operation, 7 April 1951, the skin tube esophagoplasty was successfully completed (Fig. 6).

In May 1953 this man was having increasing difficulty in swallowing, due to excessive hair growth within the skin tube. The hair was removed per pharyngoscope.

In May 1956 this patient died of a stroke. There was no evidence of recurrence of the tumor. He worked regularly up to the end. His survival time from operation was 5 years 4 months.

CASE 7. This 41 year old man was admitted 2 November 1952. He had had slight dysphagia for 6 months. Barium swallow roentgenograms showed a small filling defect in the cervical esophagus suggesting a papillary tumor on the posterior wall (Fig. 7a). The lesion was seen on direct examination; biopsy gave the diagnosis of squamous cell carcinoma.

This man was operated upon 18 November 1952. Because of the anticipated low level of the segment of esophagus to be excised, the skin flap, based on the right sternomastoid muscle, was directed somewhat obliquely downward. Further, in order to facilitate both the excision and reconstruction, the inner half of the right clavicle was excised. It was found easily possible to transect the hypopharynx above and the cervical esophagus below at what appeared to be a safe distance from the neoplasm. The larynx was preserved. After suture of the skin flap to the pharynx above and the esophagus below, direct closure of the skin defect on the left anterior part of the neck was accomplished by rotating a large segment of chest

skin upward. Pathologic examination showed that the squamous cancer extended submucosally to within 3.0 millimeters of the upper resection line (Fig. 7b). Nodes removed with the specimen contained no tumor. The esophagostoma was closed 24 January 1953 (Fig. 8a). Within 10 days this patient was swallowing easily (Fig. 8b).

During March 1954 there was a slight recurrence of dysphagia. A small nodular recurrence was seen at the upper suture line in the midline posteriorly; biopsy was positive. Cobalt 60 teletherapy was administered from 30 March to 20 April 1954; tumor dosage was estimated to be 7,600 to 8,300 roentgens. The recurrent tumor melted away.

This patient has remained perfectly well since that time and when last seen, in September 1959, was eating normally and working regularly. His voice is somewhat weak due to sacrifice of the right recurrent laryngeal nerve. His survival since first operation is 6 years 10 months.

CASE 8. This 58 year old woman was admitted 6 January 1953. In about 1944 or 1945 this woman was given "x-ray treatments" for "enlarged glands in her neck" by an irregular practitioner. In January 1952 a thyroidectomy was performed. She had a history of goiter for 17 years; she also had palpitation, shortness of breath on exertion, and heat intolerance. Her general health was much improved after this operation. During September 1952 she began to notice difficulty in swallowing solid foods. This difficulty progressed until she could take only fluids and was losing weight steadily. During the 2 weeks before coming to the hospital, she suffered from increasing difficulty in breathing and an inspiratory stridor developed. On examination, a large ulcerating lesion was seen on the anterior wall of the hypopharynx at the level of the cricoid cartilage. Her hemoglobin level was 100 per cent.

Excision of the larynx, hypopharynx, and cervical esophagus was carried out 13 January 1953. Pathologic examination showed a large fungating mass 6 by 4 centimeters with raised up, overhanging borders on the anterior wall of the esophagus adjacent to the larynx. The lines of resection were beyond the tumor. No lymph nodes could be found. The diagnosis was squamous cell carcinoma of the esophagus.

The left half of the cervical skin flap became necrotic. It was excised 27 February 1953 and replaced by a rotation pedicle graft shifted up from the anterior chest wall. Closure of the pharyngoesophagostoma was attempted 12 May 1953; healing was incomplete and a fistula developed. This was closed by local tissue shift on 8 July 1953; again some necrosis occurred and a somewhat smaller fistula remained. This fistula ultimately closed, but the patient returned in May 1954 with almost complete obstruction due to stricture at the lower end of the reconstructed esophagus. This area was dilated in May, June, and October 1954. Toward the end of 1954 a small fistula

FIG. 5. Case 5. Appearance of patient in November 1956. Laryngopharyngectomy was performed in July and in October 1949.

developed; the patient was readmitted for its treatment February 1955. Dilatation of the stricture was carried out on this occasion and on two separate occasions in April and July of that year. On 13 August 1955, closure of the fistula was again attempted without success. However, a further operation in December 1955 left her with only a pinpoint fistula into the reconstructed esophagus just above its lower end.

After that she was able to swallow liquids and soft foods and increased her weight from 89 to 108 pounds. In July 1957 she was readmitted with acute obstruction caused by a piece of meat lodged in the skin tube esophagus. This was easily removed. She was seen in November 1957 and was known to be alive as of January 1958. Since then she has become lost to follow-up. Her known survival since operation is 5 years.

CASE 9. Having suffered progressive dysphagia and hoarseness for several months, this physician was shown by direct examination and biopsy on 9 November 1953 to have an undifferentiated epidermoid carcinoma in the postcricoid region.

Cobalt 60 radiation was administered in the Toronto General Hospital 12 November 1953 to 4 January 1954; tumor dosage was estimated at 7,400 roentgens. This treatment was supplemented 13 January 1954 by a radium-loaded tube inserted in the hypopharynx and cervical esophagus for a period of 100 milligram hours. Restoration of swallowing followed this treatment for a few weeks only. About 1 February 1954, dysphagia recurred and became progressively more severe until the patient was unable to swallow even his own saliva. There was also marked dyspnea with stridor due to edema of glottic and sub-

a b

FIG. 6. Case 6. a, Appearance 15 February 1951 after cervical esophagectomy. Tracheostomy shown is temporary postoperative measure. b, Reconstruction completed 2 May 1951.

glottic areas. He was admitted to the Toronto Western Hospital 15 February 1954.

The first stage Wookey procedure was carried out 8 March 1954. The larynx, lower pharynx, and cervical esophagus were excised along with a partial bilateral neck dissection. Frozen section examination during operation showed tumor in the cut lower end of the esophagus, so a further 3 centimeters of esophagus were excised; fortunately, this area was not involved. The pathologic report indicated a very extensive epidermoid carcinoma in the hypopharynx extending 6 to 7 centimeters into the cervical esophagus. The tumor was in places 3 centimeters thick. Lymph nodes with the specimen were negative. The second stage operation was successfully performed 4 May 1954. Several tiny fistulas developed in the line of closure of the skin tube but all closed spontaneously within a few months.

In August 1954 a mass appeared in the right posterior triangle of the neck. A careful complete dissection of that triangle was carried out with sacrifice of the accessory nerve. The mass was shown to be breaking-down metastatic squamous carcinoma.

In October of 1954 this patient suffered what appeared to be a series of epileptic attacks. Investigation showed a state of hypoparathyroidism. He has been maintained since then on calcium lactate, 300 grains, and vitamin D, 100,000 units, plus 2 grains of dessicated thyroid daily.

This man is alive, well, and working regularly as of January 1960, 5 years and 10 months after his first operation (Fig. 9). During his first 2 years, dilatation of the lower anastomosis was necessary on several occasions. Hair growth has been apparent but not troublesome, despite the heavy irradiation. He now eats a full diet and has developed an excellent pharyngeal speech.

CASE 10. This 46 year old woman was admitted 3 February 1955. At the age of 30 years she underwent a seven rib thoracoplasty on the right side for pulmonary tuberculosis. Biannual check ups since then had shown no reactivation of this infection. During spring 1954 she first noticed slight difficulty in swallowing aspirin. In July 1954 progressive dysphagia became apparent. At the time of admission she could manage only very soft or liquid foods and had lost 10 pounds in weight.

Shortly after she came into the hospital, direct examination of the larynx, pharynx, and esophagus was performed under general anesthetic. A tumor was seen on the posterior wall of the hypopharynx at the level of the arytenoids; it extended downward and seemed to surround the esophagus at a lower level. The posterior wall of the trachea was bulged

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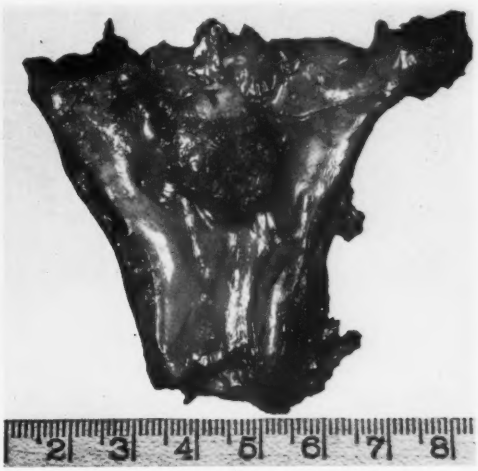

b

FIG. 7. Case 7. a, Note filling defect caused by tumor projecting from posterior wall of cervical esophagus. b, Excised pharyngoesophagus shows papillary squamous cancer on posterior wall of cervical esophagus.

forward but was not apparently invaded by the growth. Biopsy was reported as squamous cell carcinoma, well differentiated. No palpably enlarged cervical nodes were felt. Hematologic examination 9 February 1955 showed hemoglobin 69 per cent, red cell count 3,800,000, color index 0.90, white cell count 11,300; on smear, the red cells showed, moderate variation in size with an occasional microcyte, an occasional hypochromic cell, slight polychromasia, and platelets in fairly normal numbers.

On 14 February 1955 the first stage of the Wookey operation was performed with excision of the larynx, lower pharynx, and cervical esophagus plus a partial lower neck dissection on each side. The left lobe of the thyroid was carefully preserved with its blood supply via the superior thyroid vessels. The pathologic specimen (Fig. 10a) showed an ulcerating, slightly fungating mass completely encircling the hypopharynx and reaching up over the posterior surface of the larynx. On microscopic study this squamous cancer was found to be invading the attached strap muscles. The resection lines and lymph nodes examined were free of tumor. Some necrosis of the tip and lower margin of the skin flap delayed healing. During April 1955 a stricture seemed to be developing at the skin-esophagus junction, so this area was dilated several times a day.

On 26 May 1955 the second stage of the Wookey operation was successfully accomplished. By the time of her discharge from hospital, 25 June 1955, she was able to eat a full diet without difficulty and had already gained 15 pounds over her admission weight.

This patient (Fig. 10b) has remained perfectly well up to February 1960, a period of 5 years since her first operation. She has been able to eat without difficulty, has maintained her weight and strength, and does all her own housework. She does not have a pharyngeal voice but has an excellent whisper speech which is easily understood.

CASE 11. This 52 year old woman was well until April 1955 when she had an attack of acute laryngitis with hoarseness. This cleared, but she noted residual swelling in the anterior part of the neck with persistent hoarseness and progressive dysphagia. In September 1955 at the Toronto East General Hospital a biopsy was taken from within the larynx, giving the diagnosis of squamous cell carcinoma. At that time it was noted that she had a fixed right vocal cord and a nodular enlargement of the right lobe of her thyroid. She was referred to the Toronto General Hospital where radiation therapy was prescribed. A dosage of 6,240 roentgens was administered to the larynx by the cobalt 60 unit during the period from 13 September to 18 October 1955. After that, the hoarseness and dysphagia were somewhat relieved.

Early in January 1956 she was found to have nodular recurrent tumor in the right pyriform fossa. The right lobe of the thyroid was stony hard and fixed to the larynx and trachea. She was admitted 20 January 1956 and operation was performed 26 January. Because of the recent heavy radiation it was considered unwise to use a long Wookey skin flap. Instead, equal rectangular skin flaps were used, each based on the sternomastoid muscle and separated by a vertical midline incision. A very radical excision was carried out: complete neck dissection on the right side, par-

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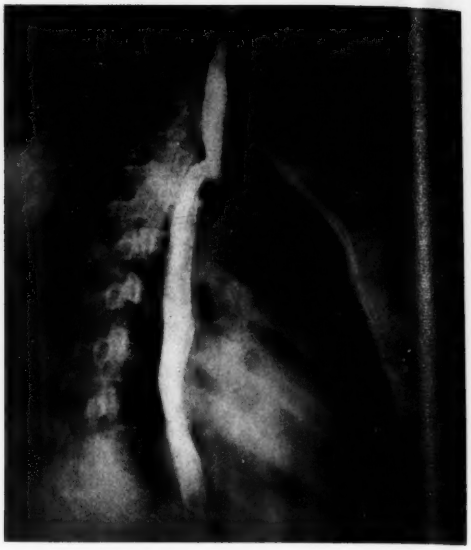

b

FIG. 8. Case 7. a, Appearance 23 March 1953, 2 months after completion of skin tube esophagus. b, Esophagogram in August 1953 outlining reconstructed cervical esophagus.

tial dissection of the left side of the neck, sternum split with anterior mediastinal dissection, laryngectomy with total thyroidectomy, plus removal of the lower pharynx and upper cervical esophagus. During the course of the operation many hard nodes were encountered, including one large mass in the mediastinum adherent to the innominate vein. A number of these nodes were submitted to frozen section and shown to contain metastatic squamous cancer. At subsequent pathologic examination all nodes were found to be replaced by tumor. After the excision the skin flaps were sutured together in the midline and joined to the pharynx above and to the esophagus below (Fig. 11a).

The specimen revealed an ulcerating squamous cell carcinoma in the subglottic portion of the larynx extending posteriorly into the cervical esophagus as far as the mucosa and laterally into the right lobe and isthmus of the thyroid. Resection lines were clear. Postoperatively this patient did very well, obtaining first degree healing of all wounds. Hypoparathyroid tetany became apparent within a few days but was readily controlled by calcium administration.

At the second stage operation 4 April 1956 the skin trough connecting pharynx and esophagus was readily converted into a tube and covered directly by skin mobilized from the two sides of the neck. A tiny fistula developed at the upper end of the skin-tube esophagus but the patient was nevertheless able to take fluids and soft foods and was allowed to go home 26 April 1956.

She was readmitted 11 May 1956 with severe dysphagia. Attempts to dilate a stricture at the lower anastomosis produced another fistula. A gastrostomy was established. At the time of discharge, 16 July 1956, all fistulas had closed spontaneously and she was once again able to take a soft diet with ease.

In January 1957 further dilatation of the stricture was required. Since then, swallowing has been maintained and has improved so that she can manage a full normal diet easily. Further, she has developed a very satisfactory pharyngeal voice with which she speaks quite clearly. Her parathyroid deficiency is controlled on calcium and vitamin D medication. Euthyroidism is maintained by 2 grains of desiccated thyroid per day.

In April 1958 a hard nodule was detected in the left lower part of the neck just above the inner end of the clavicle. Biopsy showed this to be metastatic squamous cell carcinoma. Cobalt therapy was given to this area from 23 April to 20 May 1958 in a tumor dosage of 5,000 roentgens. The mass entirely disappeared. When seen in March 1959 (Fig. 11b and c) she was wonderfully well, eating a full diet, gaining weight, and with no evidence of recurrent disease in the neck or pharynx. In September 1959 treatment with the cesium 137 unit was given to 2 nodules in the right upper part of the neck in a tumor dose of 4,000 roentgens in 2 weeks. In December 1959 treatment was given to a further nodule in the lower left supraclavicular region with cesium radiation up to 2,000 roentgens in 4 days and radium needle implant to 4,100 roentgens.

This patient is alive as of January 1960 but she undoubtedly has recurrent disease. Her survival since the first operation is 4 years.

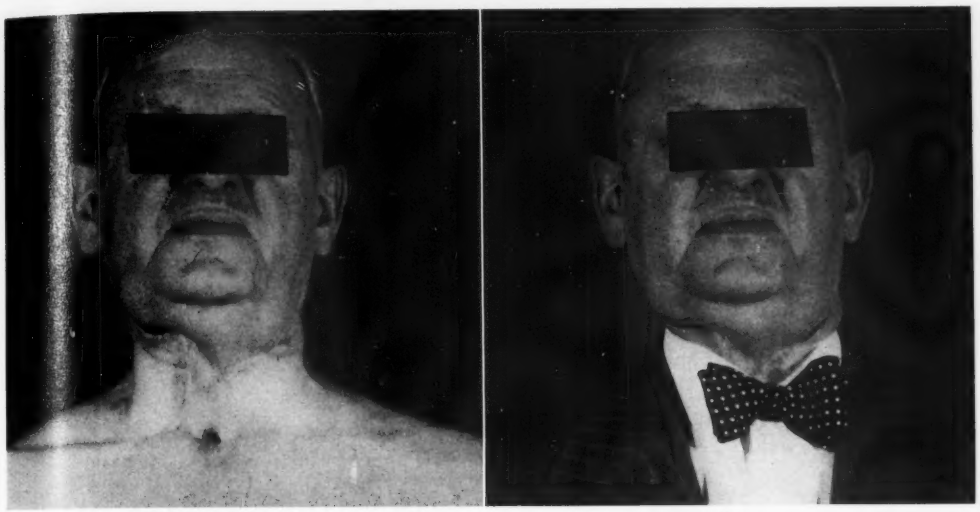

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FIG. 9. Case 9. Appearance in March 1958. Laryngopharyngectomy was performed in March and in May 1954. a, Operative scars and permanent tracheostomy. b, Satisfactory appearance when patient is clothed.

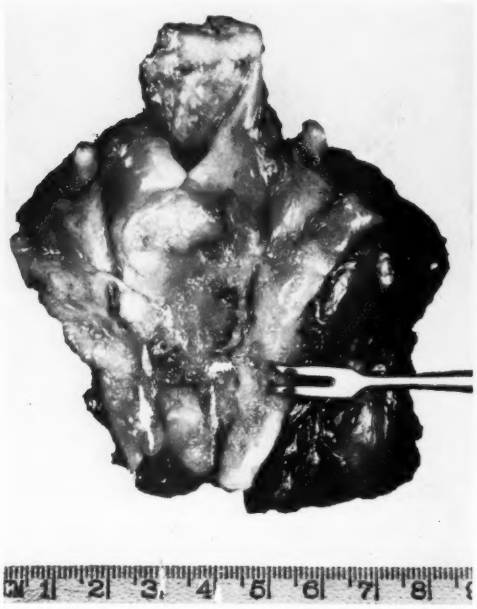
DISCUSSION

The Wookey operation as it has been described is applicable to only a limited group of tumors whose treatment necessitates the excision of a long segment of pharyngoesophagus. It must be recognized that many cases of carcinoma of the epipharynx, i.e., of the pyriform fossa, arytenoepiglottic fold, and epiglottis, can be dealt with by laryngectomy plus partial pharyngectomy with immediate direct closure of the resulting defect. It should also be pointed out that in a very few patients with tumors in this area, whose excision involves the removal of only a very short segment of pharyngoesophagus, direct end-to-end closure can be accomplished.

The Wookey procedure will be discussed under ten headings.

Selection of cases. This procedure should be applied only to cases in which the diagnosis has been proved histologically. The tumor must be of such a size and position that, after adequate excision, the skin flap can be anastomosed to the pharynx above and the esophagus below. This anastomosis can seldom be accomplished if the upper end of the lesion is higher than the base of the epiglottis, or the lower end more than 4 centimeters below the cricopharyngeus muscle. The primary tumor should be freely moveable, not fixed to prevertebral fascia, carotid sheath, or sternomastoid muscle. If cervical metastases are palpable they must be few in number, close to the primary lesion, and unilateral. There must be no evidence of distant metastases. The general condition of the patient should be satisfactory for a radical operation. The patient must be psychologically prepared to accept two operations, long hospitalization, and, possibly, permanent loss of the normal voice.

Preoperative preparation. Time should be taken to improve the patient's nutrition by feeding through a nasogastric tube or, whenever necessary, by gastrostomy. The hemoglobin should be restored to normal level by blood transfusions. Further, in emaciated patients, the blood volume should be restored to normal by giving, during the few days before operation, 500 cubic centimeters of blood by transfusion for each 10 pounds of weight loss.



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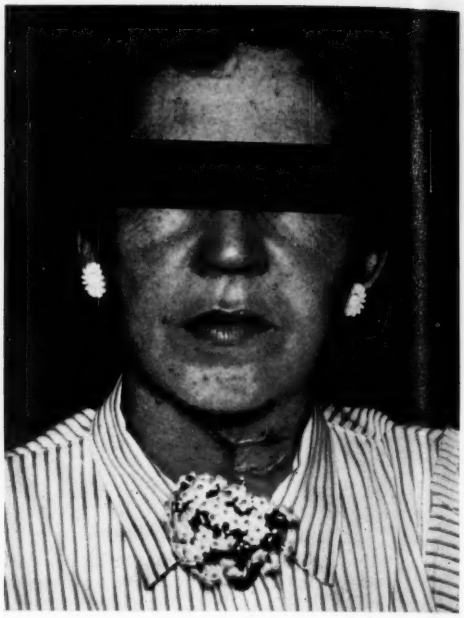

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FIG. 10. Case 10. Laryngopharyngectomy performed in February and in May 1955. a, Surgical specimen opened from behind to show ulcerating carcinoma of hypopharynx. b, Appearance July 1955 with tracheostomy hidden by blouse.

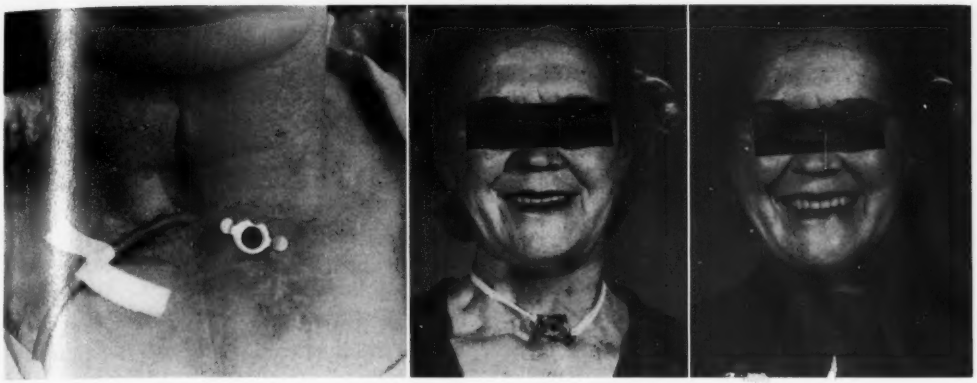
Operative technique. The skin flaps should be marked out carefully according to the anticipated size and location of the operative defect in the pharynx and esophagus. The flap should be narrower at its apex than at its base and should not be reflected back beyond the anterior border of the sternomastoid muscle on which it is based—the ipsilateral side.

Operability should be determined at an early stage by mobilizing the esophagus forward off the prevertebral fascia and palpating the lower end of the gross tumor which must be several centimeters above the thoracic inlet.

If enlarged nodes are found at operation their nature should be determined by immediate pathologic examination. When necessary, then, a full block dissection of the contralateral side of the neck may be carried out plus a partial dissection of the ipsilateral side. Complete dissection of the ipsilateral side is likely to prejudice the viability of the skin flap.

Whenever the larynx is to be removed along with the pharyngoesophagus, care should be taken to place the tracheostomy well away from the esophageal opening. This can usually be accomplished by bringing the cut end of trachea out through a separate stab wound low down in the suprasternal notch. If the two orifices are not separated in this way, the second operation may be very difficult. When the larynx and upper trachea are to be removed, something must be done about the thyroid gland. If the latter is not clearly involved, an attempt should be made to preserve at least one lobe in the hope that parathyroid function will be maintained. This can be done by mobilizing one hemithyroid along with its superior thyroid vessels and transplanting it laterally deep to the sternomastoid muscle.

In joining the skin flap to the cut end of



a b c

FIG. 11. Case 11. Laryngopharyngectomy with neck and mediastinal dissection January 1956. a, After first stage operation; note midline groove resulting from use of bilateral equal skin flaps. b and c, Appearance in March 1959; normal swallowing and good pharyngeal voice at this time.

the pharynx, the suture line is usually carried at least part way around onto the anterior wall of the pharynx, while at the lower end it has been the custom to attach the skin flap to the full circumference of the esophagus before turning back the tip of the flap toward the contralateral side of the neck. In this way, a rather deep groove is formed which is easily converted into a tube at the second operation. Of course, this folding back of the skin flap leaves a defect which Wookey was accustomed to fill with a Thiersch graft. In recent years, it has been found generally possible to close this defect directly by mobilizing the surrounding skin and utilizing simple plastic surgical maneuvers.

Postoperative management. Careful nursing is required to manage the tracheostomy, to deal with the saliva which constantly runs down from the back of the mouth, and to keep the suture lines clean and dry. The possibility of hypothyroidism or hypoparathyroidism should be borne in mind and suitable steps taken to detect and deal with these deficiencies.

The effect of preoperative irradiation. This operation is certainly much more difficult and hazardous in patients who have already undergone an unsuccessful course of therapeutic radiation. Of our 6 patients treated this way, 2 died as a result of operation; 2 had fistulas which delayed final healing for several months (Cases 9 and 11), 1 had extensive necrosis of the lower edge of the skin flap and the upper end of the trachea; only 1 had the rapid and satisfactory healing seen commonly in patients treated by operation alone. In 1 other patient, Case 8, the malign effect of irradiation previously administered to the neck area for another condition is sadly apparent.

Unless one believes that roentgenotherapy has a very good chance of curing the disease it is best to advise operation as the primary treatment. When, however, surgical treatment of radiation failures must be attempted it is probably wise to utilize bilateral equal skin flaps, as in Case 11, rather than the long unilateral Wookey flap.

Hair growth in the reconstructed skin-tube esophagus. No good solution to this problem has been found. In male patients the skin flaps should as far as possible be placed below the beard line. Neither superficial radiation therapy designed to give epilation nor the relatively large skin dose received by those who have a major course of radiation to their primary lesion have proved permanently effective in preventing subsequent

TABLE V.—OTHER SURGICAL RESULTS OF THE WOOKEY OPERATION

	Total	*Op. deaths*	*5 year survivors*
R. D. Owen (Cardiff), 1950			
Pharyngolaryngectomy	22	5	4
Cervical esophagectomy	14	4	2
Totals: No.	36	9	6
Per cent		25	17
Ronald Raven (London), 1958			
Radical surgery for carcinoma of hypopharynx	37	—	8*

*5 still living; 7 others living at 8 to 34 months.

growth of hair, as in Cases 1, 6, and 9. Wookey has expressed the opinion that hair growth in the skin tube will probably cease spontaneously after several years as a result of natural adaptation, as in Case 1.

Ability to speak after laryngopharyngectomy. Of 7 long survivors who underwent laryngopharyngectomy, 2 (Cases 9 and 11) have quite good pharyngeal speech; 1 other patient, Case 1, has a poor but intelligible speech of this sort; 2 manage very well with a whisper speech (Cases 5 and 10); 1 uses an electric vibrator to good effect (Case 4); and 1 is lost to follow-up and is, therefore, presumably speechless.

I am convinced that a satisfactory pharyngeal voice can be developed after laryngopharyngectomy with skin tube reconstruction. A competent speech therapist and the example of successful survivors should be employed as soon as the operative procedures have been successfully completed.

Other surgical results (Table V). In 1950 Owen of Cardiff published his results in a group of 36 patients with carcinoma of the hypopharynx. He had 6 five year survivors from 36 patients treated by operation. Raven of London published in 1958 his results with 37 patients of this sort treated by radical surgery. He has had so far eight 5 year survivors of whom 5 are still living. Seven others are living at 8 to 34 months. The overall results in these two series of cases are comparable to those described in this report.

Results of radiation therapy. From among 55 patients with carcinoma of the hypopharynx or cervical esophagus treated at the Toronto General Hospital with conventional radiation up to 1953, 4 survived for 3 years; only 1 lived 5 years (7). This latter patient had a squamous carcinoma on the posterior wall of the hypopharynx which was considered "too extensive for surgery." A tumor dose of approximately 6,000 roentgens was given. He obtained complete remission of symptoms and remained free of recurrent disease until his death from other causes 5 years and 7 months later.

Since June 1953 cobalt 60 therapy has been employed in all patients with this disease treated for cure. Up to 31 December 1956 a total of 17 patients with carcinoma of the hypopharynx or cervical esophagus had been so treated. One of these (Case 9) had a prompt recurrence after radiation therapy, was then treated surgically, and still survives 5 years and 10 months later. The results in the other 16 patients are summarized in Table VI. It is much too early for final judgment on this method but it does seem already apparent that no dramatic improvement in results is to be expected from it. It is my present opinion that, if a patient with carcinoma of the hypopharynx or cervical esophagus is suitable for operation, this method still offers the best chance for prolonged survival.

Alternative surgical methods. The ideal operation for carcinoma involving the pharyngoesophagus would allow immediate reconstruction of the gullet at the same time as the excision is performed. Various methods of achieving this objective have been proposed.

Rob and Bateman in 1949 reported on the use of a tantalum gauze tube covered with a sheet of fascia lata joined to the pharynx above and the esophagus below. Early results seemed encouraging and the patients were able to swallow. However, their 3 patients died within a short time from recurrence of cancer so that the long term effectiveness of the method was not established.

Negus in 1950 described a similar method but he employed a molded plastic prosthesis

covered with a split thickness skin graft. In 1952 Edgerton reported 4 cases in which skin over stainless steel mesh was used to replace the pharyngoesophagus. Good results were obtained, but the follow-up period was not over 4 months. During the same year, Cade and Reidy, discussing their experience with the Negus method, stated that ". . . the incidence of stricture is, however, common, and repeated dilatations, or even gastrostomy, become inevitable." As far as I have been able to ascertain, this criticism is amply justified and the method is losing favor.

A new technique was reported in 1954 by Goligher and Robin. In a 34 year old man with postcricoid carcinoma, excision plus immediate reconstruction of the esophagus was accomplished by bringing a long loop of the left colon up into the neck through an antethoracic subcutaneous tunnel for anastomosis with the pharynx above and the stomach below. It should be noted that the bowel was placed in the antiperistaltic direction but nevertheless functioned moderately well in swallowing. It should also be pointed out that the left colic and first sigmoid vessels were ligated and divided at a preliminary operation to encourage development of a vigorous circulation from the middle colic artery via the system of marginal vessels. The follow-up period on this case was only 2 months; at that time metastatic disease was already established.

In July 1955 I carried out a somewhat similar procedure. After cervical esophagectomy the right hemicolon with terminal ileum was brought up through a substernal tunnel in the isoperistaltic direction. The ileum was joined to the pharynx and transverse colon to the stomach. Blood supply was dependent on the right main branch of the middle colic artery. Unfortunately, the patient died at 24 hours of tension pneumothorax caused by an unrecognized tear in the right pleura. I was, however, satisfied that the procedure is technically feasible provided one is prepared to submit patient and surgeon to a very long and trying procedure in which there are many hazards, any one of which may lead to disaster.

TABLE VI.—RESULTS OF COBALT 60 THERAPY FOR CARCINOMA OF HYPOPHARYNX AND CERVICAL ESOPHAGUS IN 17 PATIENTS, JUNE 1953 TO 31 DECEMBER 1956

Survivals	*No. of patients*
At 1 year	6
At 3 years	4
Still living	3
At 4 years, 2 months	1
At 3 years, 6 months	1
At 3 years, 2 months	1

*Included in the 17 is 1 "failure" treated surgically, living and well.

Jack in 1955 described a single successful case in which the stomach and thoracic esophagus were mobilized through the left side of the chest so that they could be advanced upward into the neck, allowing reanastomosis of the esophagus to the pharynx after excision of the larynx and cervical esophagus. Blood supply was maintained via the right gastric and right gastroepiploic vessels. If dependable longitudinal anastomoses, such as were present in this case, could be shown to occur generally, this method would be a very good solution to the problem.

The newest method to have been tried has been devised by Seidenberg and his associates. This group demonstrated in dogs the feasibility of replacing the cervical esophagus by a transplanted free segment of jejunum revascularized by anastomosis of its artery and vein to suitable vessels in the neck. They described 1 human case in which the method was used; unfortunately the patient died of a cerebrovascular accident on the seventh postoperative day. Postmortem examination showed that the grafted bowel loop had remained viable and that the esophagojejunal anastomoses were well healed.

In 1957, Hyde working in the laboratory of Toronto General Hospital investigated the idea of using a transplanted revascularized free segment of colon to replace the cervical esophagus in dogs. A single success-

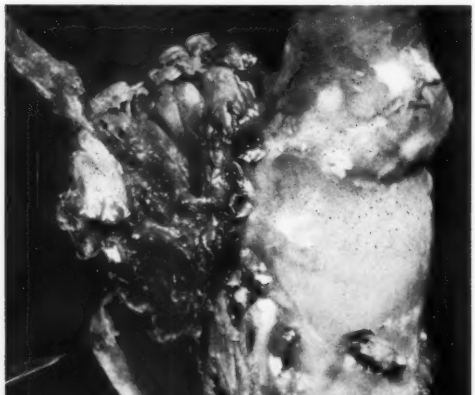


FIG. 12. Specimen from dog sacrificed at 2 months after successful free transplant of colon segment to replace cervical esophagus. Reconstructed esophagus functioned normally; vascular anastomoses of colonic to cervical vessels remained patent.

ful result was obtained (Fig. 12). It appeared that further application of this method must await development of a more reliable method of anastomosing small blood vessels. This concept of using autogenous bowel transplants to replace the esophagus is a good one and merits further investigation.

All of these techniques are interesting but none has proved of value; for the present, the Wookey operation remains the safest and surest method in the cases in which it is applicable.

SUMMARY AND CONCLUSION

The Wookey operation has been described as a method of dealing with carcinoma of the hypopharynx and cervical esophagus. From among 44 patients treated this way there have been 9 (24 per cent) 5 year survivals. Details are given of these 9 patients plus 2 others who have survived for 4 years. These results are compared with those of two other large surgical series and with those obtained at the Toronto General Hospital by radiation therapy.

Technical details of the Wookey operation are discussed and some observations are made about the effect of preoperative irradiation, hair growth within the skin tube, and the ability to speak after laryngopharyngectomy.

Alternative surgical procedures are described which have as their objective immediate reconstruction of the cervical esophagus at the time of excision.

It is concluded that, in cases of carcinoma of the hypopharynx or cervical esophagus considered suitable for operation, excision offers the best chance for prolonged survival, and that, until some method of one stage reconstruction of the cervical esophagus becomes clearly established, the Wookey procedure remains the safest and best.

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BILIARY INTESTINAL ANASTOMOSIS USING A JANEWAY TYPE DUODENAL TUBE

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ANASTOMOSIS of the common duct to the intestinal tract has occupied the interest of surgeons for many years. The problems involved in a satisfactory anastomosis are those of stricture and, to a lesser extent, reflux of intestinal contents into the biliary tree. Stricture of the line of anastomosis is the usual cause of failure of operations for joining the biliary tract to the intestine.

An investigation of biliary-intestinal anastomosis was undertaken in dogs, using a full thickness Janeway type tube made from a flap of duodenal wall. This tubular structure was then anastomosed to the common duct, and the animals were followed up for periods up to 14 months. Circumferential suture was created in some animals by using an end to end anastomosis. In other animals, a linear incision was made in the common duct and an end-to-side anastomosis was created. In the latter type of anastomosis, the common duct distal to the anastomosis was divided in some animals and in others was simply occluded by ligature. In this way, the effectiveness of using an intestinal tube was studied with different types of biliary intestinal anastomoses as is illustrated in Figure 1.

MATERIAL AND METHODS

Using mongrel dogs weighing from 12 to 18 kilograms, an anastomosis was made between the biliary tract and the duodenum in two operations. At the first operation, cholecystectomy was performed in order to prevent the gallbladder from becoming the focus of biliary tract infection. The common duct was then partially constricted by a cotton ligature as close as possible to the duodenum. As a result of this preliminary operation, the common duct became dilated, often to 1.5 centimeters in diameter, making subsequent anastomosis easier.

At the second operation, 4 to 5 weeks later, a biliary-intestinal anastomosis was constructed. A loop of duodenum was selected midway between the pylorus and the ligament of Treitz. At this point, a full thickness tube was made from a flap of duodenal wall, similar to the method used in a Janeway gastrostomy. The flap of duodenum was roughly 4 centimeters in width and 6 to 8 centimeters in length. The flap was closed in one layer and later in two, so that the resulting tubular structure could accommodate a size 16 French polyethylene tube.

After construction of the tube, anastomosis to the common duct was performed in three ways. The first anastomosis was end-to-end, joining the intestinal tube to the cut end of the common duct. The second was anastomosis of the intestinal tube to a linear incision in the common duct, with division and ligation of the common duct distal to the anastomosis. The third method was the same as the second except that the common duct was ligated in continuity by a silk ligature distal to the anastomosis and not divided. All anastomoses were performed over an 8 centimeter length of No. 16 French polyethylene tubing which was used as a stent. The stent was secured by one cotton suture to keep it from shifting. The duodenal tube was sutured to the common duct with a single row of cotton sutures which included the full thickness of both the duodenal tube and the common duct.

No obstruction of the duodenum was

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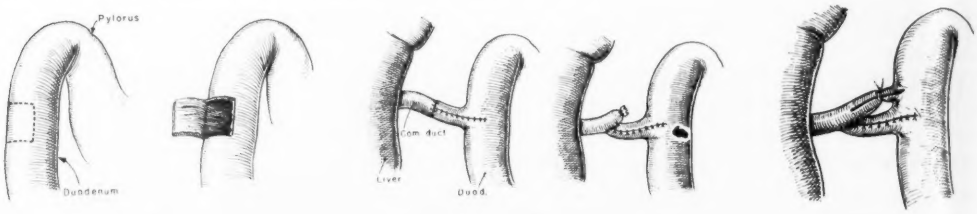

FIG. 1.

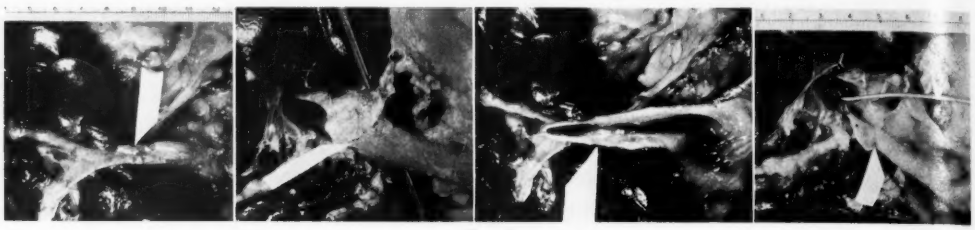

FIG. 2.

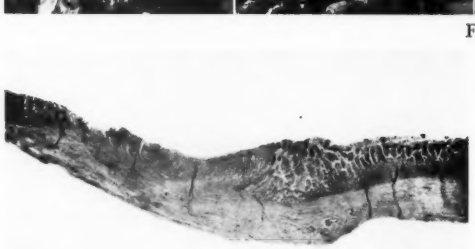

FIG. 3.

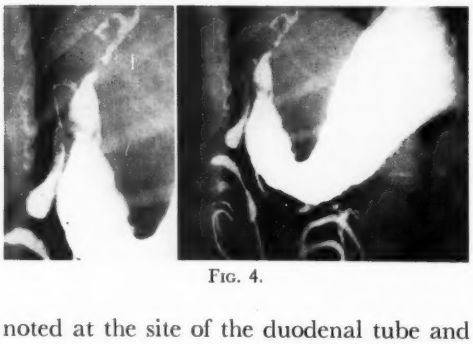

FIG. 4.

FIG. 1. The full thickness flap of duodenum is fashioned into a tube as in a Janeway gastrostomy. a, End-to-end anastomosis; b, end-to-side anastomosis; and c, end-to-side anastomosis without division of the common duct are illustrated in this schematic drawing.

FIG. 2. Photographs of end-to-end and end-to-side anastomoses are shown as found at sacrifice. They are also shown after opening the ducts through the anastomotic sites. The anastomotic sites are marked by white arrows.

FIG. 3. Microphotograph of end-to-end intestinal biliary anastomosis. The duodenal mucosa is seen on the right. In the center of the photograph is the anastomosis. The common bile duct is seen on the left. There is no scar formation.

FIG. 4. Roentgenograms of an animal given a barium meal. The liver radicals are seen filled with barium.

noted at the site of the duodenal tube and no enteroenterostomy was necessary to bypass this area. Without any type of bypass, reflux of intestinal contents into the biliary tract could occur and was subsequently demonstrated by roentgenogram after a barium meal.

There were 13 animals in which the three types of anastomoses were studied. Five animals were used for the anastomosis of the end of the intestinal tube to the end of the common duct. Four animals were used for the end-to-side anastomosis with division of the common duct distal to the anastomosis. Four animals were used for the end-to-side anastomosis and ligation of the common duct in continuity. The 9 animals used in performance of the first two types of anastomoses were sacrificed between 12 and 14 months after the anastomosis was created

(Fig. 2). Of the 4 animals in whom the third method was used, 3 were sacrificed between 6 and 9 months, and 1 died from an unknown cause at 3 months. This animal was not discarded, because the findings were of interest when contrasted to the other animals of the group.

RESULTS

The results in these biliary intestinal anastomoses were recorded according to five criteria (Tables I, II, and III). The first was the size of the anastomosis as observed at sacrifice; and, from the size, an estimation of the amount of stricture formation was made. The other criteria were the nutritional status of the animal at sacrifice, gross and microscopic changes in the liver, the microscopic appearance of the anastomosis, and finally, gross changes in the biliary tract, such as calculus formation, cholangitis, and dilatation.

In estimating stricture formation, the size of the anastomosis at sacrifice was compared to the original size of the anastomosis created at operation (Fig. 2). The original anastomosis was created over a No. 16 French polyethylene tube used as a stent, and thus had a minimum circumference of 1.6 centimeters. Only one anastomosis was obliterated by stricture in the 13 animals. This was an end-to-side anastomosis in which the common duct distal to the anastomosis had been ligated and not divided. At autopsy, the common duct was shown to have been re-established, and the anastomosis was obliterated. This animal died 3 months after construction of the anastomosis from an undetermined cause.

In the remaining 12 animals the smallest anastomosis was 0.9 centimeter, the largest 2.5 centimeters, most of them as large or larger than the original anastomosis.

The nutritional status of the animals at sacrifice was excellent in all except the 1 with stricture of the anastomosis. This animal lost weight. The other animals gained from 10 per cent to 75 per cent of their original body weight.

Examination of the livers of all of the animals showed them to be grossly normal. However, microscopic examination revealed that there was evidence of cirrhosis in 2 animals and of pericholangitis in 4 others. Six animals had normal livers on microscopic examination and 1 was not examined.

The microscopic appearance of the anastomosis revealed that it was covered by mucous membrane in all but 2 animals (Fig. 3). One of the 2 showed a hyalinized membrane at the junction of the duodenal flap with the common duct; the other was the animal with the strictured anastomosis.

The final criterion by which the results of anastomosis were judged was evidence of gross changes in the biliary tract, such as calculus formation, dilatation, or cholangitis. In 1 animal, calculi were found in the biliary tract. In 1 other, the common duct appeared dilated. None of the other animals showed any notable change in the gross appearance of the common duct. Of the 4 animals who had end-to-side anastomosis of the duodenal tube to the side of the common duct and in whom the duct was ligated distal to the anastomosis, all showed reconstitution of the common duct with patency of the lumen at the site of ligature. The ligature was No. 00 silk and could be demonstrated at autopsy lying beside the common duct and no longer occluding it.

Reflux of duodenal contents into the biliary tree was demonstrated by roentgenogram of 8 animals after a barium meal (Fig. 4). Barium could be seen in the biliary tree in all 8 animals. The films were taken about 1 hour after the barium meal.

DISCUSSION

The efficacy of intestinal-biliary anastomosis using a Janeway type tube made from a flap of duodenum was investigated in 13 dogs. It was found that the method was successful in 11 animals, in that there was little evidence of stricture. This was true in both end-to-end and end-to-side anastomoses. In 2 animals there was evidence of stricture. One animal showed a 50 per cent decrease

TABLE I.—RESULTS IN END-TO-END ANASTOMOSIS BETWEEN THE CUT END OF THE COMMON DUCT AND THE DUODENAL TUBE

	Circumference of anastomosis, cm.	*Weight gain at sacrifice, per cent*	*Microscopic appearance of liver*	*Microscopic appearance of anastomosis*	*Gross changes in biliary tract*	*Reflux*
1	0.9	18	Normal	Covered by mucous membrane	None	Not investigated
2	1.5	30	Perichol-angitis	No mucous membrane, hyalinized	None	Present on roentgenogram
3*	2.0	42	Cirrhosis	Covered by mucous membrane	Calculi in common duct	Present on roentgenogram
4	2.0	33	Normal	Covered by mucous membrane	None	Present on roentgenogram
5	1.5	42	Perichol-angitis	Covered by mucous membrane	None	Present on roentgenogram

*The animal with biliary cirrhosis, one of the largest anastomoses, and largest weight gain, also had calculi in the common duct.

TABLE II.—RESULTS IN END-TO-SIDE ANASTOMOSIS BETWEEN A LINEAR INCISION IN THE COMMON DUCT AND THE END OF THE DUODENAL TUBE AND DIVISION OF THE COMMON DUCT BEYOND THE ANASTOMOSIS

	Circumference of anastomosis, cm.	*Weight gain at sacrifice, per cent*	*Microscopic appearance of liver*	*Microscopic appearance of anastomosis*	*Gross changes in biliary tract*	*Reflux*
6	1.5	33	Normal	Covered by mucous membrane	None	Present on roentgenogram
7	2.5	50	Normal	Covered by mucous membrane	None	Present on roentgenogram
8	2.0	50	Normal	Covered by mucous membrane	None	Present on roentgenogram
9*	1.5	75	Cirrhosis	Covered by mucous membrane	Dilated	Present on roentgenogram

*The animal with cirrhosis had an adequate anastomosis, a dilated common duct, and, paradoxically, the greatest weight gain.

TABLE III.—RESULTS IN END-TO-SIDE ANASTOMOSIS BETWEEN A LINEAR INCISION IN THE COMMON DUCT AND THE END OF THE DUODENAL TUBE WITH LIGATION OF THE COMMON DUCT BEYOND THE ANASTOMOSIS

	Circumference of anastomosis, cm.	*Weight gain at sacrifice, per cent*	*Microscopic appearance of liver*	*Microscopic appearance of anastomosis*	*Gross changes in biliary tract*
10*	Obliterated by stricture	None	Grossly normal, not examined microscopically	Obliterated	Common duct reopened, grossly normal
11	1.7	10	Pericholangitis	Covered by mucous membrane	Common duct reopened, grossly normal
12	1.8	10	Normal	Covered by mucous membrane	Common duct reopened, grossly normal
13	1.5	10	Pericholangitis	Covered by mucous membrane	Common duct reopened, grossly normal

*The only stricture occurred in this group. All common ducts reopened at the point of ligature.
No roentgenograms were taken for reflux in this group.

in the circumference of the anastomosis, which was end-to-end or circumferential in type. The other animal had complete stricture of the anastomosis. This occurred in a dog with end-to-side anastomosis in which the common duct had been ligated in continuity and subsequently reopened.

It was thought that if the common duct were allowed to reopen after the anastomosis had been made, there might be some evidence of stricturing of the anastomosis. For that reason, end-to-side anastomosis was performed and the duct was ligated in continuity beyond the anastomosis. These common ducts all reopened and in the group of 4 animals prepared in this way the one strictured anastomosis did occur. However, the other three anastomoses appeared adequate up to 9 months later.

Other effects of malfunction of the anastomosis were noted. There were 2 animals with biliary cirrhosis; in one calculi were found in the common duct, and in the other the duct appeared dilated. The anastomoses were 2.0 and 1.5 centimeters in circumference, both apparently adequate in size.

The nutrition, as evidenced by the gain in weight, and the healing of the anastomosis, as demonstrated on microscopic examination, appeared satisfactory. The presence of reflux in all of the animals having roentgenograms was of interest. No attempt was made to prevent reflux by creating a bypass, and it is assumed that duodenal contents was almost constantly present in the biliary tree.

SUMMARY

Using dogs, an intestinal-biliary anastomosis was created by the use of a Janeway type tube made from a flap of duodenum. Three types of anastomosis were made. The first was end-to-end, the second was end-to-side with division of the common duct beyond the anastomosis, and the third was end-to-side with ligature of the common duct beyond the anastomosis. The anastomoses were generally successful when examined up to 14 months later. Evidences of stricture and malfunction of the anastomosis were present, but most animals did well.

FACTORS INFLUENCING THE MORBIDITY AND MORTALITY IN THE OLDER AGED PATIENT UNDERGOING PULMONARY SURGERY

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AN INCREASING NUMBER of older aged patients are now undergoing pulmonary operations. This is the result of the increased longevity of the general population and the greater incidence of malignant disease of the lung that now obtains in our present day society. The peak incidence of this disease, according to life insurance statistics (2), occurs in the age group of patients between 55 and 74 years old.

It is now generally accepted that the older patient will tolerate most surgical procedures well if concurrent and complicating diseases are eliminated, yet an extensive review by Cole revealed that with such thoracic operations as esophagectomy and pneumonectomy the mortality rate was significantly higher in the aged. This has been emphasized further by Hepper and Bernatz who reported a mortality rate of 29.6 per cent for pneumonectomy in 27 patients 70 years of age and older. However, Campbell and Langston in a study of 31 patients more than 60 years old concluded that the elderly patient could undergo extensive intrathoracic surgical procedures if the resection of lung tissue was as conservative as possible. That conservation of functioning lung tissue is an important consideration in lessening mortality in the older patient is stressed by the results of Price Thomas who reported a mortality rate three times as high after pneumonectomy as that after lobectomy in patients 50 years of age and older.

Since many of the patients in the sixth, seventh, and eighth decades often have associated degenerative diseases as well as decreased physiologic reserve brought about by the process of aging, the present study was undertaken to determine the factors other than the operation per se which influence the mortality after pulmonary operation in this group. From this study an increased alertness to the problems peculiar to this age group might be obtained.

The records of all patients undergoing thoracotomy for the treatment of pulmonary, pleural, or mediastinal disease at the Veterans Administration Research Hospital and on the author's service at Passavant Memorial Hospital were reviewed. One hundred twenty-six consecutive patients 55 years of age and older were found available for study. The age distribution of the group is shown in Figure 1. The mean age was 62.5 years and the median age was 62 years. The procedures performed in these patients are shown in Figure 2. The diseases found were bronchogenic carcinoma in 90; granuloma in 10; metastatic malignant tumor in 7; tuberculosis in 5; chronic pneumonia in 2; and miscellaneous disorders in 12. The clinical records were reviewed to determine the preoperative status, the postoperative 30 day mortality, and the morbidity of these patients.

Preoperative status. The cardiovascular system was judged to be clinically normal in 99 patients and abnormal in 27. The clinical abnormalities were hypertension in 37 cases; cardiac murmur in 9; arrhythmia in 9; cardiac failure in 2; and severe angina in 2. On review of the electrocardiograms, the tracings were interpreted as normal in 83 and abnormal in 43 patients. Ab-

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normalities included cardiac arrhythmia in 9; residual of myocardial infarct in 9; bundle branch block in 4; and nonspecific changes in 21. The arrhythmia present was auricular fibrillation in 5 patients, multiple extrasystoles in 3, and pulsus bigeminus in 1.

Respiratory status was evaluated clinically and also by appropriate laboratory study in the majority of patients. The physiologic data obtained by the use of the 1 second vital capacity test in 78 and the maximum breathing capacity test in 62 patients, respectively, are illustrated in Figures 3 and 4. Correlation of the objective data with the clinical and roentgenographic findings was utilized in an attempt to determine preoperatively the maximum resectional procedure that could be tolerated by the individual patient.

Review of the other systems in these patients revealed the presence of diabetes mellitus in 5, a history of gastrointestinal bleeding in 5, cirrhosis in 4, and varying degrees of benign prostatic hypertrophy in over 50 per cent of the group.

Mortality. There were 9 deaths within the 30 day postoperative period in the 126 patients, a mortality of 7.1 per cent. The distribution according to age is seen in Figure 1 and according to the procedure performed in Figure 2. The causes of death in the 4 patients who underwent pneumonectomy were cardiac failure preceded by the development of an arrhythmia (atrial flutter) and concomitant respiratory insufficiency in 2, acute myocardial infarct in 1, and pulmonary edema associated with multiple pulmonary infarcts in 1.

The causes of death in the 2 patients who had a lobectomy were bilateral pneumonia in 1 and complications that followed a gastric resection for massive bleeding from multiple acute gastric ulcers in the other.

In the patients who died after exploration only—those with nonresectable malignant disease—death was related to the procedure in 2 patients: intrapleural bleeding occurred in 1 and atelectasis with respiratory insufficiency and cardiac failure in the other. The

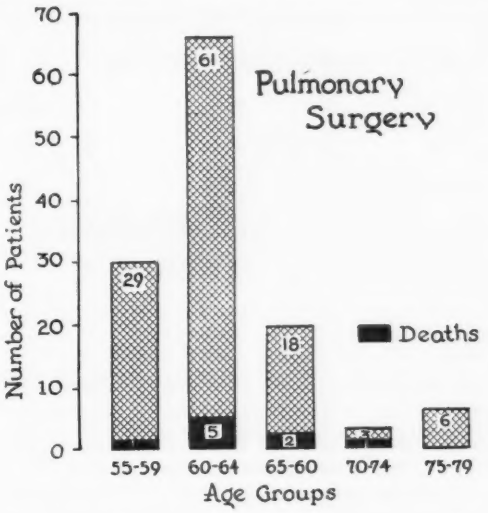

FIG. 1. Age distribution and 30 day postoperative mortality in 126 patients undergoing pulmonary surgery.

demise of the remaining patient in this group was the result of a ruptured abdominal aneurysm.

Morbidity. The majority of the nonfatal complications were related to the cardiovascular and respiratory systems, although gastrointestinal and urinary complications were troublesome. These complications included 18 instances of arrhythmia; 1 each of myocardial infarction and phlebitis; 5 each of atelectasis and persistent air space; 4 of respiratory insufficiency; 3 of empyema and bronchopleural fistula; 6 of ileus; 1 of gastrointestinal bleeding; and 5 of urinary retention. The development of an arrhythmia was the most common event. The types and frequency of occurrence are shown in Table I. Respiratory complications were seen most often in the patients with lobectomy, although retention of tracheobronchial secretions was frequent after any procedure in this age group.

DISCUSSION

The mortality and morbidity in this series of older aged patients is not dissimilar to that in younger individuals undergoing thoracic operations. The correction or control

FIG. 2. Procedures performed and 30 day mortality in 126 patients 55 years of age and older.

of pre-existing physiologic abnormalities and the prompt treatment of postoperative complications appeared to be essential in the successful outcome of any procedure.

In 6 patients who died it was difficult to determine any single factor responsible for the fatal outcome. In each a combination of cardiac and respiratory factors were present. Which weighed heavier in the scale, myocardial failure or insufficient pulmonary reserve, remained elusive.

Diminished pulmonary reserve is a major problem in the older patient. The evaluation of the patient's reserve by pulmonary function studies gives objective data that, when correlated with the patient's exercise tolerance, general physical condition, and roentgenographic findings, permits a reasonable impression as to the magnitude of the procedure that might be tolerated. Tailoring the resectional procedure, for example, a lobectomy or sleeve resection of the main bronchus in place of pneumonectomy, in the light of this evaluation as well as to the disease may on occasion avoid a postoperative fatality.

TABLE I.—POSTOPERATIVE CARDIAC ARRHYTHMIAS IN 121 PATIENTS*

No. patients	*Procedure*	*Runs of premature ventricular contractions*	*Premature auricular beats*	*Auricular flutter or fibrillation*
29	Pneumonectomy	2	0	7†
32	Lobectomy	1	0	5
3	Segmentectomy	0	0	0
12	Wedge resection	0	0	0
6	Miscellaneous	0	0	0
39	Exploration only	1	1	3
121	Total	4	1	15

*Five of the 126 patients in the series have been excluded, since auricular fibrillation was present preoperatively.
†Includes 2 patients who died with heart failure, atrial flutter and respiratory insufficiency.

In these older patients the retention of tracheobronchial secretions is of more serious import than in the younger patients. Not only is any respiratory complication superimposed on a lessened respiratory reserve a serious event but also fatigue from frequent and often ineffectual coughing may result in the general deterioration of the patient. The use of wetting agents, expectorants, tracheal aspiration, and bronchoscopy may be employed satisfactorily in many of the patients, but the use of a tracheostomy is an invaluable adjunct in the prevention and management of retained secretions. An elective or emergency tracheostomy was employed in approximately 10 per cent of the patients in this series. Not only is the maintenance of a clear airway and evacuation of secretions facilitated but also a more efficient respiratory effort is obtained. Elective tracheostomy is now recommended in all debilitated patients as well as in those with a markedly reduced pulmonary reserve. If not performed at the time of the surgical procedure, its early employment is advised in patients in whom inadequate evacuation of secretions is present. If delayed until it becomes mandatory, its performance may be life-saving but on occasion will fail to reverse the trend of events in such desperate situations. Another advantage of a tracheostomy is that it facilitates the use of a mechanical respirator when assisted or controlled ventilation is necessary.

Gastrointestinal ileus may complicate respiratory insufficiency in these patients. Gastric dilatation, especially after a right pneumonectomy, may embarrass respiratory exchange acutely due to compression of the remaining functioning lung by the elevated diaphragm. This must be relieved promptly by intubation and aspiration. The routine and prolonged use of nasal oxygen may contribute to such dilatation through excessive air swallowing. It has been our practice to

discontinue oxygen therapy as soon as possible, even in the patients who have had pneumonectomy, since its injudicious use may contribute to rather than avoid postoperative difficulties.

The presence of cardiac embarrassment in the face of respiratory insufficiency was an ominous development. Prompt use of digitalization, diuretics, and fluid restriction was on occasion of no avail. The development of and failure to control a serious cardiac arrhythmia in 2 patients who died raises the question as to the significance of this occurrence in the older patient. In 13 other patients, when the arrhythmia was converted to a normal sinus rhythm or its rate controlled by appropriate medication, no serious difficulty developed. Likewise, in those patients who were fibrillating preoperatively, but in whom the rate was controlled by digitalis therapy, no difficulty was noted from the presence of the arrhythmia in the postoperative period. However, the high incidence of postoperative cardiac arrhythmias in the older age group is of interest and has been noted by others. In the present series an arrhythmia occurred 20 times in 121 patients, 16.1 per cent. This is in contrast to its infrequent occurrence in younger patients. It was not seen to develop in any patient less than age 55 at either hospital in this series. Nor was it seen by the author in a review of 101 patients undergoing pneumonectomy for the treatment of pulmonary tuberculosis—all but 4 of whom were 54 years of age or younger—although its development is more frequent after a pneumonectomy than after lesser procedures.

The cause of a postoperative arrhythmia in any 1 patient was obscure. Preoperatively the history of a previous arrhythmia or the presence of frequent premature ventricular contractions appeared to be the only significant features that might presage the occurrence of a postoperative atrial flutter or fibrillation. Clinical and electrocardiographic studies otherwise were of no value in suggesting in which patient the complication might develop.

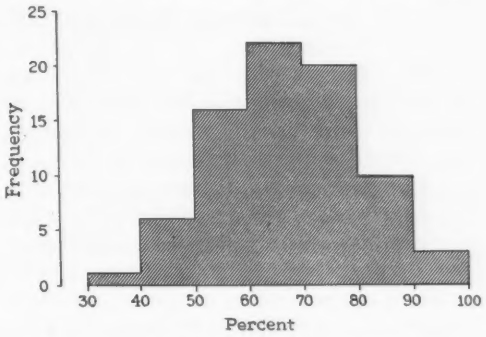

FIG. 3. Results of the 1 second timed vital capacity test expressed in per cent of normal in 78 patients.

At the present time routine prophylactic therapy with either digitalis, as often advocated in the older patient, or quinidine, as suggested by Hurt and Bates, is not utilized. Preoperatively, digitalis therapy is reserved for those patients who have been in cardiac failure or who are fibrillating at the time of admission to the hospital. Quinidine sulfate is given prophylactically to those individuals who have a history of a previous cardiac irregularity. Likewise it is used in those patients who have frequent runs of premature ventricular contractions before operation or in whom they develop

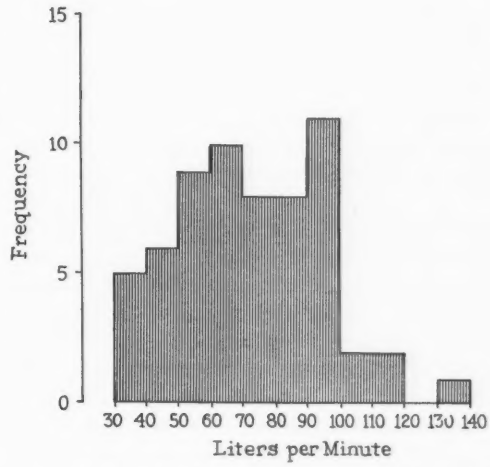

FIG. 4. Results of the maximum breathing capacity test expressed in liters per minute in 62 patients.

in the postoperative period. In the untreated patients in whom auricular fibrillation develops postoperatively but who remain essentially asymptomatic except for the rapid irregular pulse, it is our policy to convert the patient to normal rhythm by the use of the quinidine sulfate. If flutter is present or if the arrhythmia is associated with a fall in blood pressure, restlessness, diaphoresis, and dyspnea, prompt intravenous digitalization is our procedure of choice. Administration of oxygen and occasionally vasopressors also may be indicated temporarily in these patients. We believe this expectant treatment in the light of the present series is a reasonable course of action.

SUMMARY

A series of 126 patients 55 years of age and older who underwent pulmonary operations was reviewed. There were 9 deaths, 7.1 per cent, within the 30 day postoperative period. Cardiovascular and respiratory problems accounted for 8 of the deaths and also produced the majority of the nonfatal complications. Respiratory insufficiency and ineffectual cough with retained secretions were major causes of respiratory difficulties. The use of tracheostomy in many such patients was valuable. Development of a cardiac arrhythmia was a common postoperative complication, especially in the older patient undergoing pneumonectomy, although it was seen after lesser procedures as well. Treatment with either quinidine sulfate or digitalis has been employed successfully when this complication has occurred. Prophylactic therapy with either drug is not routinely recommended.

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CERVICAL CONIZATION DURING PREGNANCY

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THE OBJECTIVE of diagnostic cervical conization during pregnancy is to ascertain if invasive carcinoma is present in the cervix when that possibility exists and when a complete diagnosis apparently cannot be obtained in any other way. The advantages of prompt, accurate diagnosis over delay until the pregnancy is over are: (1) the obvious one of the opportunity to begin therapy as soon as feasible, and (2) the special advantage of a diagnosis early enough to avoid delivery through the cervix if invasive cancer is found and it has been decided to deliver the baby before institution of treatment. We assume that delivery through a cervix that harbors invasive cancer is inadvisable but not contraindicated in the presence of intraepithelial carcinoma.

It was anticipated that the operation posed fetal as well as maternal risks. An important question to be answered was whether the advantages of early and exact diagnosis were worth the risk to the fetus. We concluded that each case must be decided on its own merits.

To our own knowledge, ours is the largest experience with this procedure and should be of value to others in establishing the place of the conization operation during pregnancy. This report is based on 50 conizations performed upon 49 patients at the University of Miami Jackson Memorial Hospital. Whereas earlier reports from this institution were concerned with staff patients, this report includes 5 private patients. Seventeen of the operations were performed during the first trimester of pregnancy, 16 in the middle trimester, and 17 in the last trimester. The weeks of gestation during which the operation was performed ranged from approximately the third week to the thirty-ninth week. The patients' ages varied from 16 to 43 years.

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INDICATIONS AND DIAGNOSES

These 50 conizations were performed because of (1) punch biopsy diagnosis of intraepithelial carcinoma of the cervix or (2) a positive cervical cytology report that could not be satisfactorily explained. In earlier publications, Ferguson, Schulman, Demick, and Offen (4, 5, 7) have explained why a punch biopsy diagnosis of intraepithelial carcinoma of the cervix is not acceptable as a final diagnosis, and why a positive cytologic result demands a large and adequate specimen of the cervix unless invasive cancer is found in smaller specimens.

Intraepithelial carcinoma of the cervix. Twenty-six of the operations were performed because of a punch biopsy diagnosis of intraepithelial carcinoma of the cervix. Of these 26 cases, the cone specimens contained the same preinvasive lesion in 17 instances, invasive cancer in 3, while only dysplasia remained in 4 specimens and cervicitis in 2.

In 7 cases, the indication was a punch biopsy diagnosis of dysplasia. In 4 of these, the cone specimens contained intraepithelial carcinoma of the cervix, in 2, dysplasia, and in 1, cervicitis.

Six patients had a punch biopsy diagnosis of cervicitis but because of a positive cytologic result, which was thought to be unexplained, a conization was performed. Four of the cone specimens showed only dysplasia, 1, cervicitis, and 1, intraepithelial carcinoma.

Although an effort was made to obtain punch biopsy specimens from all patients who were to have a conization, they were not obtained from 11 patients and the indi-

cation for the operation in those cases was a positive cytologic result. Invasive cancer was found in 2 of the cone specimens and intraepithelial carcinoma in 6. In 8 of the 11 patients whose conization was performed on the basis of a positive cytologic result, a positive result was obtained on 2 or more occasions.

TECHNIQUE

The technique in our earlier conizations of the cervix lacked some of the refinements that were added later. For the last 2 years the operation has usually been performed by one of the variations of the operation described by Offen and Ferguson and by Scott, Welch, and Blake. Infiltration of the cervix with at least 100 milliliters of hemostatic solution, excision of an adequate specimen with a cold knife, and light electrocauterization of the bleeding points were the important components of the operation. It was thought best to omit curettage of the endocervical canal when the patient was pregnant. Hormone therapy has not been used as an adjunct.

MATERNAL COMPLICATIONS

Operative and postoperative blood loss. The conization operation in pregnancy can usually be performed today with but little blood loss. Thirty-eight of the 50 operations were accompanied by an estimated blood loss of 100 milliliters or less.

Seven patients lost between 100 and 200 milliliters of blood. Five of these 7 patients were the only pregnant patients who had a readmission to the hospital because of bleeding from the conization site. They were readmitted on the seventh to the fourteenth postoperative day. The treatment was usually either the packing of plain gauze against the cervical defect, the local application of acetone, or a combination of the two. Each patient needed transfusion on readmission.

The 5 patients who lost more than 200 milliliters of blood were operated upon before our present technique was developed or when this technique was not employed. The estimated blood losses in this group were 300, 500, 700, and, in 2 cases, 1,500 milliliters. There was no correlation between the week of gestation and the quantity of blood loss. There was, however, a tendency for the patients operated upon in the later weeks of pregnancy to receive more careful care, for example, longer periods of hospitalization and bed rest.

Miscellaneous complications. There were no maternal deaths. One patient, in the seventh week of pregnancy, had a pulmonary infarct on the ninth postoperative day. On the fourteenth postoperative day, while under heparin therapy, she aborted and lost 3,000 milliliters of blood. It could not be accurately determined if the source of the bleeding was the uterine cavity, the conization site, or both. Two patients had severe cervical lacerations at delivery, which were repaired.

It was not recognized that the operation caused prolongation or shortening of labor. One patient had difficulty in achieving full dilatation and required cervical incisions when dilatation stopped at 7 centimeters.

Because so many of the operations were performed relatively recently, meaningful observations cannot be made on the ultimate effect on the patient of conization during pregnancy. Although the first operation was performed in December 1954, 74 per cent of the operations were performed in 1958 and 1959. No outstanding difficulties have been encountered, such as, evidence of infertility or important degrees of cervical stenosis. Healing took place with as remarkable rapidity in pregnant as in nonpregnant women.

FETAL COMPLICATIONS

It was anticipated that conization during pregnancy would expose the fetus to the risk of abortion and premature labor. We have thought it fairest to be critical and to assume that all abortions and deliveries of premature babies were due to the conization.

Of the 50 pregnant women with conizations reported herein, 8 are still undelivered and the pregnancies are proceeding un-

eventfully. Twenty-four have delivered healthy mature infants.

Seventeen of these operations were performed in the first trimester of pregnancy and 16 in the second trimester. There were 5 cases of abortions classified as loss of a fetus of less than 500 grams. The first followed external radiotherapy for carcinoma. The second occurred after conization but, as the uterus was sounded the day before conization by an intern who did not realize the patient was pregnant, the conization may not have been responsible for the loss. The third was a missed abortion, more likely due to the excision of the corpus luteum during an exploratory colpotomy in the seventh week of pregnancy performed with a preoperative diagnosis of possible tubal pregnancy; the conization was performed 1 week after the excision of the corpus luteum. The fourth, previously referred to, occurred in the patient who was under heparin therapy because of pulmonary infarction, and the conization must be blamed for the abortion. The fifth abortion occurred in the patient who had conization of the cervix during the tenth week of pregnancy and aborted 3 weeks later.

Three of the pregnancies produced immature fetuses of 500 to 999 grams. Of these 3, as was expected, 1 abortion occurred when radiation therapy for cancer was started after the conization; the second pregnancy ended 10 weeks after conization with a 650 gram infant that expired in 7 hours; the third infant weighed 995 grams at birth and now is 13 months old and well.

Ten pregnancies of the 50 have terminated with the delivery of a premature baby, weighing from 1,000 to 2,500 grams. All infants except 1 survived.

If the premature and immature infants are combined into one group of 12, the premature birth rate is 27 per cent. The hospital premature incidence is consistently maintained at the high figure of 14 per cent, making it difficult to distinguish between spontaneous premature labor and labor induced by conization. That 10 of the 12 immature-premature group survived is largely to the credit of a premature center in the hospital. Without this facility more of these infants might have died.

To summarize the fetal losses, there were 8 of the 50 pregnancies that did not produce a surviving fetus. Eight of the 50 patients are still undelivered. Four of the fetal losses may not have been due to the conization. Two of the losses might be presumed to have been doomed by radiotherapy, a third by excision of the corpus luteum in early pregnancy, while the sounding of a pregnant uterus might be implicated in the fourth. Beecham and Andros reported no fetal losses in 26 conizations performed during pregnancy.

COMMENT AND MISCELLANEOUS CASES

A conization attempted in the thirty-ninth week of pregnancy had to be abandoned because of inability to expose the cervix adequately enough to perform the operation with safety. Redundant vaginal mucosa, obesity, and a high cervix provided obstacles that could not be overcome.

It was not recognized that 1 patient was in the early weeks of gestation, and conization, dilatation, and curettage were planned in that order. During the dilatation the uterus was perforated, and therefore the curettage was not performed. She delivered uneventfully at term.

Three conizations were performed in the thirty-eighth and thirty-ninth weeks of pregnancy. Delivery was uncomplicated.

One patient had a conization of the cervix in 2 successive pregnancies. The first operation was performed during the third week of pregnancy because of 2 Papanicolaou class V smears. An intern, unaware that the patient might be pregnant, sounded the uterine cavity. This first cone showed intraepithelial carcinoma. She aborted after the operation. Three weeks after operation, a punch biopsy specimen was obtained, and it could not be decided if it showed intraepithelial carcinoma or invasion. She became pregnant at once and refused another

conization until the twenty-second week of pregnancy. Three weeks after the second conization, she delivered a 1,048 gram baby who survived. The diagnosis on the second cone was intraepithelial carcinoma.

An interesting observation concerns the 2 patients who bled so much during punch biopsy that they had to be admitted to the hospital, yet they subsequently tolerated a conization. They lost 200 milliliters and 350 milliliters of blood from the punch biopsy. In both, a diagnosis of intraepithelial carcinoma was made from the punch specimen. Four and 8 days later they had conization with a 200 milliliter loss in each case. A third patient lost 250 milliliters from a punch biopsy, but the bleeding was controlled so well with a pack that she was not hospitalized. Two weeks later she had a conization and lost 1,500 milliliters of blood; the excessive blood loss was believed due to the use of an inadequate amount of hemostatic solution.

We have found that the degree of positiveness in a positive cytologic result cannot indicate the necessity for conization. Although invasive carcinoma tends to provide class IV and class V smears, and lesser degrees of neoplastic change class III smears, the inconsistencies that exist are dangerously misleading.

For reasons proposed in earlier reports (2, 3) we consider the Papanicolaou class III smear as "positive." Because of the lack of agreement that exists on the importance of the class III cancer smear, the following observations are made: A great majority of these patients had more than 1 positive cytologic smear, and in some patients the degree of positiveness varied, showing class III at one time and a greater degree of positiveness at another. Of the conization patients who had class III smears, and only class III smears, the cone diagnosis proved to be intraepithelial carcinoma in 10 instances, dysplasia in 5, and cervicitis in 1.

To evaluate this operation, the purpose of which is to detect invasive carcinoma, the 5 cases were studied in which invasion was found in the cone specimen. The diagnosis of invasion was established in the following weeks of gestation: 6, 21, 21, 37, and 38. In each case the establishment of this diagnosis afforded an opportunity to avoid vaginal delivery. If the collection of an adequate specimen had been postponed until delivery or some time in the postpartum weeks there would have been a delay in each case and the delay could be considered undesirable in 3 of the cases. In an experience with 50 cases, it is apparent that from 3 to 8 fetuses may have been sacrificed to gain this advantage of earlier diagnosis.

SUMMARY AND CONCLUSIONS

An experience with 50 conizations during pregnancy shows that the operation may be performed with little risk to the mother. There is a risk to the fetus, as 8 of the pregnancies have failed to produce a surviving baby. By correction of fetal loss data, only 3 fetal deaths can be blamed on the conization operation. Each case of possible carcinoma of the cervix must be evaluated by weighing the advantages of an accurate diagnosis during the existent week of pregnancy against the postponement of that diagnosis until some later date to be chosen by the surgeon.

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GENERAL FACTORS INFLUENCING THE INCIDENCE AND MORTALITY OF ACUTE PERFORATED GASTRODUODENAL ULCERS

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IT HAS BEEN CONVENIENT to speak of the complications of peptic ulcer according to 4 categories: perforation, hemorrhage, obstruction, and intractability. Little interest, however, has been shown in determining what factors, if any, predispose a given ulcer patient to any one or more of these complications.

At the Cook County Hospital, only patients with complications of peptic ulcer are admitted to the wards. An effort was made to learn as much as possible from over 16,000 records of patients discharged between 1936 and 1955 with a diagnosis of peptic ulcer.

Each potential record was screened according to an outline prepared as a syllabus divided into 6 major sections: general data, symptoms, physical findings, laboratory data, treatment, and pathologic findings. It became necessary for practical purposes not only to present each complication of ulcer separately but also to subdivide the presentation still further into one of the 6 sections of the syllabus or combinations thereof. The items screened from the hospital record for this report included the following:

1. Case number
2. Admitting diagnosis
3. Age
4. Date of admission
5. Race and sex
6. Birthplace (93 nations; 48 states)
7. Residence (idem)
8. Occupation
9. Military service
10. Family history (using standard nomenclature code for specific diagnoses)
11. Past medical history (idem)
12. Past surgical history (idem)
13. Dietary habits
14. Marital status
15. Sleeping habits
16. Weight
17. Home environment
18. Hospitalization (preoperative and postoperative days)

Two registered nurses, who had previously worked as medical record historians, surveyed the records for a period extending over 20 years. An arbitrary decision was made to accept only those records containing a proved ulcer complication, defined as the objective demonstration of an ulcer by roentgenography, gastroscopy, operation, or autopsy. In difficult cases the final acceptance of such a case was made by one of us.

RESULTS

Incidence. One thousand nine hundred and four cases of perforated peptic ulcer were accepted for analysis out of a 20 year total of 8,451 patients hospitalized for ulcer treatment. There were 1,372,117 total admissions to the hospital during this period, or an incidence of perforation of 138 per 100,000 admissions. Acute perforation of a peptic ulcer accounted for 22.5 per cent of all admissions for confirmed peptic ulcer.

In 37.8 per cent the perforations were classified as gastric (719 cases), and duodenal perforations represented 62.2 per cent

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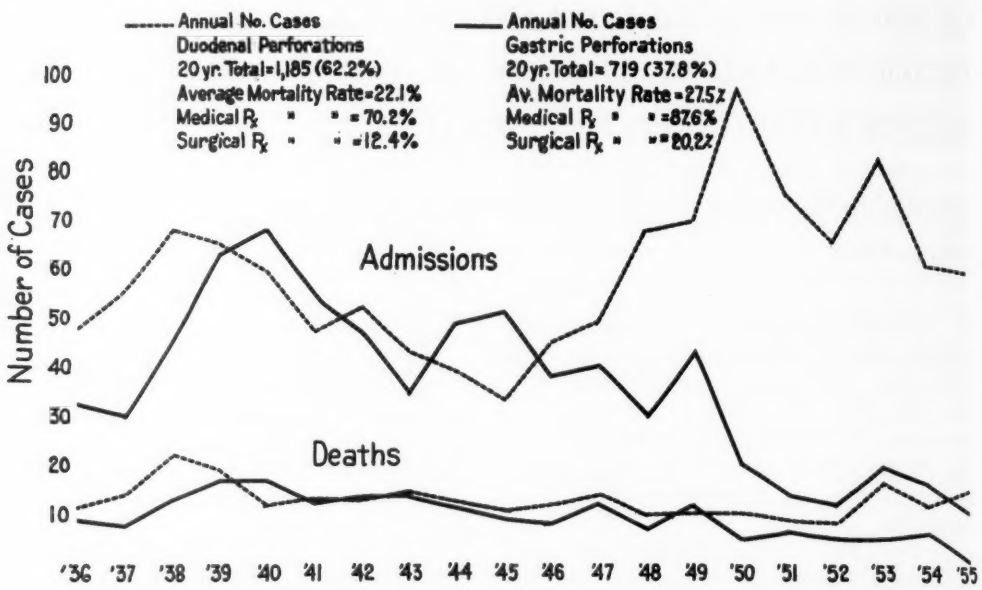

FIG. 1. The number of patients with peptic ulcer perforation, gastric and duodenal, admitted between the years 1936 and 1955 inclusive. The marked increase in the occurrence of duodenal perforations and decrease in gastric perforations since 1945 is striking. The mortality rate for duodenal perforations showed a relative improvement since 1945, but gastric perforations did not.

(1,185 cases). Five of the 20 years surveyed showed a significant increase in duodenal perforations (1938, 1939, 1940, 1949, and 1950). A significant decline in the annual incidence of acute perforated gastric (peptic) ulcers was apparent from 1945 to 1955 (Fig. 1).

Mortality. The total mortality rate for perforated peptic ulcer for the period 1936 through 1955 was 24.0 per cent. The average annual mortality rate for the gastric group was 27.5 per cent and for the duodenal group 22.1 per cent.

In the group of 719 patients with gastric perforations, 43 were treated by medical, nonoperative measures alone and 30 were unrecognized prior to autopsy; 64 of these 73 patients died, making the mortality rate 87.6 per cent. For the 646 patients with gastric perforations which were treated by operative means, the mortality rate was 20.2 per cent.

In the group of 1,185 patients with duodenal perforations, 145 were treated medically and 48 were diagnosed only at autopsy; 137 of these 193 patients died, a mortality rate of 70.2 per cent. For the 992 patients with duodenal perforations surgically treated, the mortality rate was 12.4 per cent. The mortality rate for duodenal perforations declined significantly in the second decade; however, the mortality rate concerning gastric perforations remained essentially unchanged.

Site of perforation. Figure 2 illustrates the sites of the perforations in 1,638 patients surgically treated. Forty-three of these, or 2.6 per cent, were on the posterior wall of the stomach or duodenum; all of the others were on the anterior surface. Altogether, 992 cases involved the following portions of the duodenum: 158 were on the anterior surface of the duodenal bulb; 5 were on the posterior surface of the duodenal bulb; 744 were found on the anterior surface of the first portion of the duodenum; and 15 were on the posterior surface. There were 6 in the second portion of the duodenum and 2 in the third.

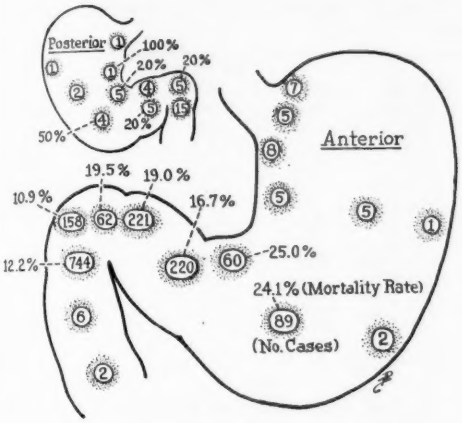

FIG. 2.

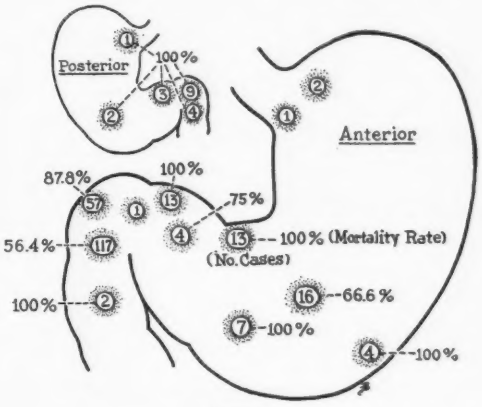

FIG. 3.

FIG. 2. The sites of 1,638 surgically treated gastroduodenal perforations. The number of cases are encircled as craters; the percentages refer to mortality rates of significant sized groups. An increased mortality rate was found as one progressed from the duodenum to the cardia.

FIG. 3. The sites of 256 nonsurgically treated gastroduodenal perforations; in 10 patients the site of perforation was in doubt. The number of cases are encircled as craters; the percentages refer to the mortality rate of significant sized groups.

Arbitrarily included in the duodenal cases were 62 perforations on the anterior surface of the pyloroduodenal juncture.

Figure 2 also locates the sites of 646 surgically treated gastric perforations. Two hundred and twenty-one occurred in the pylorus and 220 in the pyloric antrum. There were 169 perforations of the fundus: 60 on the lesser curvature side, 2 on the greater curvature side, 89 on the anterior wall, and 18 on the posterior wall. The body of the stomach was the site of 11 anterior and 4 posterior perforations. The cardia of the stomach was the site of 20 anterior perforations distributed as indicated in Figure 2, and 1 posterior perforation. No examples of both a duodenal and a gastric perforation were encountered in the same patient; however, there were many examples of perforated ulcers which were coexistent with bleeding or stenosing ulcers located at another site.

Mortality rates were calculated for groups of cases according to site of perforation. The lowest mortality rate was 10.9 per cent for 158 perforations of the duodenal bulb. There were no deaths recorded in 15 perforations of the posterior duodenal wall; however, this is a relatively small group. The mortality rate for perforations of the anterior wall of the first portion of the duodenum, the most frequent site, was 12.2 per cent; for perforations of the pyloroduodenal juncture the mortality rate was 19.5 per cent. Gastric perforations at all sites had significantly higher mortality rates than did duodenal perforations; viz., the pyloric perforations had a 19.0 per cent mortality; those of the pyloric antrum, 16.7 per cent; of the lesser curvature, 25.0 per cent; and of the anterior wall of the fundus, 24.1 per cent.

The sites of 256 medically treated and nontreated perforated peptic ulcers are shown in Figure 3. These were confirmed by roentgenogram, subsequent operation, or autopsy data. The most frequent site for this group was the anterior wall of the first portion of the duodenum; these patients had the lowest mortality rate of all the conservatively treated patients—56.4 per cent. The consistently poor results for all others so treated is indicated in Figure 3. In 10 patients the exact site was doubtful.

Age. All patients' ages, except 3 unknown,

TABLE I.—INCIDENCE AND MORTALITY OF GASTRODUODENAL PERFORATIONS ACCORDING TO AGE DECADE

Age decade, yrs.	Per cent* of Cook County hosp. census	Gastric				Duodenal			
		No. of cases	Per cent of 1,904 cases	No. of deaths	Per cent mortality	No. of cases	Per cent of 1,904 cases	No. of deaths	Per cent mortality
0– 9	†	2	0.11	2	100	8	0.42	7	87.5
10–19	6.5–5.5	4	0.21	0	0	13	0.68	0	0
20–29	11.4–13.9	76	4.0	6	7.9	179	9.4	9	5.0
30–39	13.7–15.4	150	7.9	20	13.3	310	16.2	34	11.0
40–49	16.6–15.8	175	9.2	36	20.8	282	14.8	55	19.5
50–59	19.4–16.3	185	9.7	67	36.2	215	11.3	62	28.8
60–69	16.5–15.3	89	4.7	39	43.8	124	6.5	64	51.7
70–79	9.2–11.7	29	1.5	21	72.5	43	2.2	23	53.5
80–89	2.1–3.7	9	0.47	7	77.8	11	0.57	8	72.7
Totals		719	37.7	198	27.5 (avg.)	1,185	62.2	262	22.1 (avg.)

*Listed as percentages at the beginning and end of the study, respectively.
†Not calculated because these 10 cases occurred in approximately 150,000 pediatric admissions.

TABLE II.—INCIDENCE AND MORTALITY OF GASTRODUODENAL PERFORATIONS ACCORDING TO RACE AND SEX*

Race and sex	Per cent† Cook County hosp. census	Gastric				Duodenal			
		No. of cases	Per cent of 1,895 cases	No. of deaths	Per cent mortality	No. of cases	Per cent of 1,895 cases	No. of deaths	Per cent mortality
White male	42.2–28.4	526	27.7	149	37.2	777	41.0	186	23.9
Colored male	19.5–29.5	152	8.0	25	16.4	335	17.6	39	11.6
White female	20.9–13.8	21	1.1	14	66.6	39	2.0	23	59.9
Colored female	15.7–28.2	17	0.9	9	52.9	28	1.4	10	35.6
Totals		716	37.8	197	27.4 (avg.)	1,179	62.2	258	22.1 (avg.)

*Nine cases of peptic perforation in oriental males are not included in this table; analysis made of white and colored races only.
†Listed as percentages at the beginning and end of the study, respectively.

were classified according to decades as listed in Table I. Their incidence and mortality rates are averages for the 20 year experience. The extremes in hospital census of age decades for medical and surgical services involved are also listed. For the ages of 30 through 49 years, the occurrence of perforations exceeded the general hospital census significantly; in all other years it was either equal to or less than this census.

In all decades the number of duodenal perforations exceeded the number of gastric perforations. The peak came 2 decades earlier in patients with duodenal perforations. There were 10 perforations in patients under 6 months of age and 20 in patients past the age of 80 years.

With the exception of the first decade of life, each decade showed a progressive rise in the mortality rate, from a 0 mortality in the 10 to 19 year old age group rising to more than 70 per cent in those past the age of 80 years.

A comparison of the first and second halves of the 20 year period studied established certain trends. The proportion of duodenal perforations increased after 1945 with a corresponding decrease of gastric perforations (Fig. 4). The mortality rate for duodenal perforations showed a marked decline after 1945 in each decade from age 20 to 69 years. There was an increased number of patients less than 9 and more than 69 years old; these age extremes did not show this improvement; despite that, the total lowering of mortality rate for duodenal perforations resulted in a decline from 27.8 per cent to 17.7 per cent (Fig. 5). There was no parallel lowering of the mortality rate of gastric perforations.

Season. There was no significant predisposition for perforations to occur in any month or groups of months (Fig. 6). The fewest cases, 122, occurred during the month of February, and the maximal number, 199, during May. The greatest number of gastric

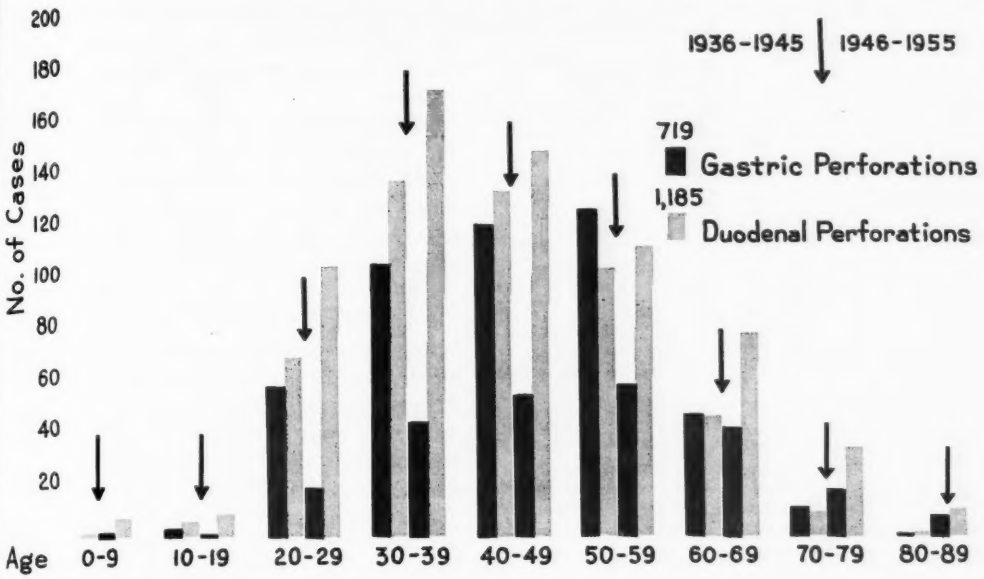

FIG. 4. A comparison of age trends in gastric and duodenal perforations, between the decade preceding and following 1 January 1946. Gastric perforations occurred with almost equal incidence to duodenal perforations in the years 1936 through 1945; since then, the relative rise of duodenal perforations in all age decades was noted. An increased incidence of infants and patients past 69 years of age was noted after 1946.

perforations, 75, occurred in July, and the fewest, 50 cases, in September. For duodenal perforations, the peak month was May with 125 cases, and the lowest was February with 72 cases. Gastric perforations showed a more uniform number per month than did duodenal perforations. Arranged as to the four seasons of the year, spring (April, May, and June) was the time of the most gastroduodenal perforations (504 cases), whereas the winter season (January, February, and March) was the time of the fewest (432 cases).

There was no significant trend of mortality rates according to the months of the year. The highest and lowest mortality rates for gastric ulcer occurred in March and December, respectively; for the duodenal perforations it was September and February, respectively.

Race and sex. The racial classification used was: white (Caucasian), colored (Negro), yellow (Oriental), red (Indian), and brown (Pacific). The vast majority of perforations occurred in both sexes of the white and colored races. There were 6 cases of duodenal perforation and 3 of gastric perforation in Chinese males; there were no instances in yellow females or in Indian or brown races. Because of the small number of cases in the Oriental race, they were deleted from further consideration.

The white male predominated in all categories (Table II), accounting for 68.7 per cent of all perforations; white males constituted 42.2 per cent of admissions to the services involved at the beginning of this period of study and 28.4 per cent at the end. The number of white males with gastric perforations has shown a progressive decline, out of proportion to his decreased hospital census over the last 10 years of the survey. White males now account for less than 10 per cent of all gastric perforations as compared to the 20 year average of 27.7 per cent (Fig. 7). Despite a decline in hospital census,

TABLE III.—INCIDENCE AND MORTALITY RATE OF GASTRODUODENAL PERFORATIONS IN WHITE AND COLORED MALES ACCORDING TO AGE DECADES

Age decade	Per cent* hosp. census Cook County	Gastric				Duodenal			
		No. of cases	Per cent of 1,904 cases	No. of deaths	Per cent mortality	No. of cases	Per cent of 1,904 cases	No. of deaths	Per cent mortality
0–9	†								
White		0	0	0	0	1	0.05	1	100
Colored		2	0.1	2	100	4	0.20	4	100
10–19									
White	2.1–0.5	1	0.5	0	0	7	0.35	0	0
Colored	1.5–2.0	4	0.20	0	0	5	0.25	0	0
20–29									
White	2.7–1.5	45	2.4	3	6.6	107	5.6	7	6.5
Colored	2.8–5.1	27	1.4	1	3.7	79	4.2	2	2.5
30–39									
White	3.9–2.5	90	4.7	11	12.2	181	9.5	25	13.8
Colored	4.1–5.3	54	2.8	8	14.7	117	6.1	7	5.9
40–49									
White	6.4–4.1	137	7.2	29	21.7	183	9.6	39	21.3
Colored	4.1–5.3	34	1.7	4	11.7	73	3.8	10	13.7
50–59									
White	9.9–5.2	156	8.2	55	35.2	165	8.6	48	21.9
Colored	3.2–5.1	18	0.9	4	22.2	37	1.9	7	18.9
60–69									
White	9.4–6.3	74	3.9	31	41.8	99	5.2	52	52.5
Colored	1.9–3.0	8	0.4	4	50.0	19	1.0	6	31.6
70–79									
White	5.1–5.5	19	1.0	15	79.9	29	1.5	11	38.0
Colored	1.0–1.8	5	0.25	2	40.0	4	0.2	3	75.0
80–89									
White	1.1–1.5	7	0.35	5	71.5	5	0.25	4	80.0
Colored	0.1–0.6								

*Listed as percentages at the beginning and end of the study, respectively.
†Not calculated because these 7 cases occurred in approximately 150,000 pediatric admissions.

the white male with a duodenal perforation continued to head the list.

The colored male accounted for 25.6 per cent of all perforations and for 19.5 per cent and 29.5 per cent of the admissions at the beginning and end of the study, respectively. The percentage of gastric perforations was 8.0 per cent for the colored male compared to 27.7 per cent for the white male. In the colored male the incidence was 17.6 per cent for duodenal perforations compared to 40.8 per cent for the white male. The occurrence of duodenal perforations in colored males averaged between 6 and 8 per cent during the period of 1936 to 1940. This incidence has progressively risen to currently account for more than 30 per cent of all duodenal perforations (Fig. 7). The rise in admission census of the colored male was 10.0 per cent for the period of the study. At the same time, the occurrence of gastric perforations in the colored males has remained essentially unchanged.

In the white female, the incidence of 3.1 per cent of all perforations compared to a hospital census which started at 20.9 per cent and finished at 13.8 per cent; 21 of these perforations were gastric and 39 were duodenal. As can be seen from Figure 7, in the white female, in recent years, a slight rise in incidence of duodenal ulcer perforations has occurred, e.g., 7 per cent of all cases in 1955, but a decline in incidence in gastric perforations.

The colored female represented 15.7 per cent and 28.2 per cent of admissions at the beginning and the end of the study, respectively. Seventeen cases of gastric and 28 of duodenal perforations occurred in this group; this accounted for 0.9 per cent and 1.4 per cent, respectively, of all perforations. The colored female also showed a slight rise

in occurrence of duodenal perforations in more recent years, but much less than the 12.5 per cent increase demonstrated in admission census.

The peak of occurrence of perforated duodenal ulcer was in the same decade for white and colored males. For gastric perforation it was 2 decades later for the white than the colored male (Fig. 8). All patients past the age of 79 with perforations were white males.

There was a 37.2 per cent and 23.9 per cent mortality rate, respectively, for gastric and duodenal perforations in the white male; for the colored male the figures were 16.4 per cent and 11.6 per cent, respectively. The mortality rates for the white female were 66.6 per cent and 59.9 per cent for gastric and duodenal perforations, respectively. The comparable mortality figures for the colored female were 52.9 per cent and 35.6 per cent.

Because of the marked difference in mortality rates between the white and colored races, the incidence and deaths within each decade were tabulated as were the extremes of the admission census for the medical and surgical services (Table III). The females were deleted from this analysis because of their small number. In patients aged 20 through 59 years, gastroduodenal ulcers perforated more frequently in the white male than anticipated on the basis of admission census; after age 70, the reverse was true. This was true in the colored male only aged 30 through 39 years and by a small margin; in all other decades an ulcer perforated in the colored male in a ratio equal to or less than his admission census. For 8 of the 12 decades with significant numbers of patients with perforations, the mortality rate was lower for the colored male than for his white contemporary. After 50 years of age, the white male made up 29.0 per cent of all perforations, whereas the colored male accounted for 4.65 per cent.

Birthplace. The birthplace of all but approximately 12 per cent of the entire group of patients was recorded on the clinical

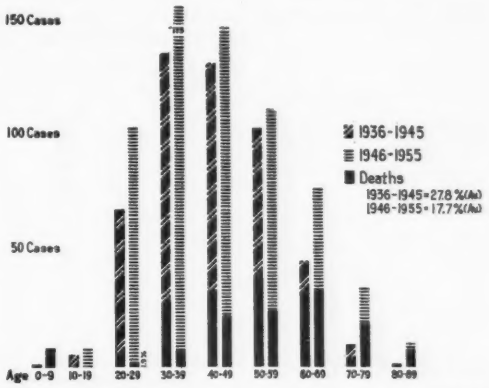

FIG. 5. A comparison of the mortality rate for duodenal perforations in the decades preceding and following 1 January 1946. Except for the decades which included infants and patients past 69 years of age, there was consistent lowering at every age level. Despite the influx of the extremes of age with attendant high mortality rates, the average mortality for duodenal perforation fell 10.1 per cent between the two decades.

record. Approximately 30 per cent of the gastric perforations and 24 per cent of the duodenal perforations occurred in patients born in the State of Illinois.

The incidence of duodenal compared to gastric perforation was relatively higher in patients migrating from the Southern states (Table IV). In the case of patients of European extraction, the number of gastric perforations was greater than the number of duodenal perforations, completely reversing the usual ratio of duodenal to gastric perforations.

The mortality rates from different areas likewise varied significantly. Patients of southern birth had a 15 per cent mortality rate for both gastric and duodenal perforations. Those born in the North had a 28.6 per cent mortality for gastric and 24.1 per cent mortality for duodenal perforations. Patients of European extraction had a 37.3 per cent mortality rate for gastric and a 33.3 per cent mortality rate for duodenal perforation. The other ethnic groups included in Table IV were too small for comparative analysis.

Occupation. Sixty-five per cent of those admitted to the hospital were dependents, the

TABLE IV.—GEOGRAPHIC DISTRIBUTION OF BIRTHPLACE OF PATIENTS WITH GASTRODUODENAL PERFORATIONS: RELATIONSHIP TO INCIDENCE AND MORTALITY

	Gastric				Duodenal			
Birthplace	*No. of cases*	*Per cent of 1,904 cases*	*No. of deaths*	*Per cent mortality*	*No. of cases*	*Per cent of 1,904 cases*	*No. of deaths*	*Per cent mortality*
United States	471	24.7	111	23.3	829	43.5	167	20.2
North	293	15.4	84	28.6	470	24.7	113	24.1
South	178	9.3	27	15.0	359	18.8	54	15.0
Americas (except U.S.A.)	8	0.4	0	0	25	1.3	10	40.0
Europe	166	8.7	62	37.3	162	8.5	54	33.3
Asia	4	0.2	0	0	6	0.3	0	0
Unknown	70	3.7	25	35.7	163	8.4	31	19.0

TABLE V.—INFLUENCE OF OCCUPATION UPON INCIDENCE AND MORTALITY RATES OF PATIENTS WITH GASTRODUODENAL PERFORATION

		Gastric				Duodenal			
Occupation	*Per cent Cook County hosp. census*	*No. of cases*	*Per cent of 1,904 cases*	*No. of deaths*	*Per cent mortality*	*No. of cases*	*Per cent of 1,904 cases*	*No. of deaths*	*Per cent mortality*
Dependent	65.0	89	4.6	45	50.6	159	8.3	72	45.2
Nonskilled laborer	10.7	143	7.5	54	35.3	389	20.4	67	17.2
Semiskilled laborers	12.5	99	5.2	18	18.2	178	9.3	20	11.2
Skilled laborers	8.8	81	4.2	22	27.2	131	6.8	24	18.3
White collar group	2.1	27	1.3	6	22.2	49	2.5	9	18.3
Professional group	0.6	3	0.15	1	33.3	13	0.65	2	15.4
Unknown		277	14.5	52	18.8	266	13.9	68	25.3

majority being wards of a charity, unemployed, housewives, children, relief workers, students, or old age pensioners. In 12.9 per cent of these patients an ulcer had perforated. Duodenal perforations constituted the larger number of cases. The mortality rate was 50.6 per cent for the gastric group and 45.2 per cent for the duodenal group (Table V).

Nonskilled laborers accounted for 10.7 per cent of admissions; this group was made up of factory workers, porters, janitors, construction helpers, domestics, freight handlers, watchmen, section hands, gardeners, and peddlers. This group represented 27.9 per cent of all perforations. Duodenal perforations were more numerous than gastric, but the mortality rate for duodenal perforation in this category was half that for gastric perforations, 17.2 per cent versus 35.3 per cent.

Semiskilled laborers made up 12.5 per cent of admissions; these were construction workers, waiters, cooks, drivers, bartenders, policemen, firemen, sailors, bellhops, service station attendants, elevator operators, soldiers, motormen and conductors, and mailmen. Perforated ulcers developed in 14.5 per cent. The number of duodenal perforations exceeded the gastric; the mortality rate for gastric perforation was 18.2 per cent and for duodenal, 11.2 per cent.

Eleven per cent of all perforations and 8.8 per cent of admissions were among skilled laborers; this included carpenters, painters, mechanics, machinists, barbers, bakers, dressmakers, masons, plumbers, printers, welders, butchers, steam fitters, and maintenance men. The ratio was less in favor of the gastric group, but the mortality was in favor of the duodenal group.

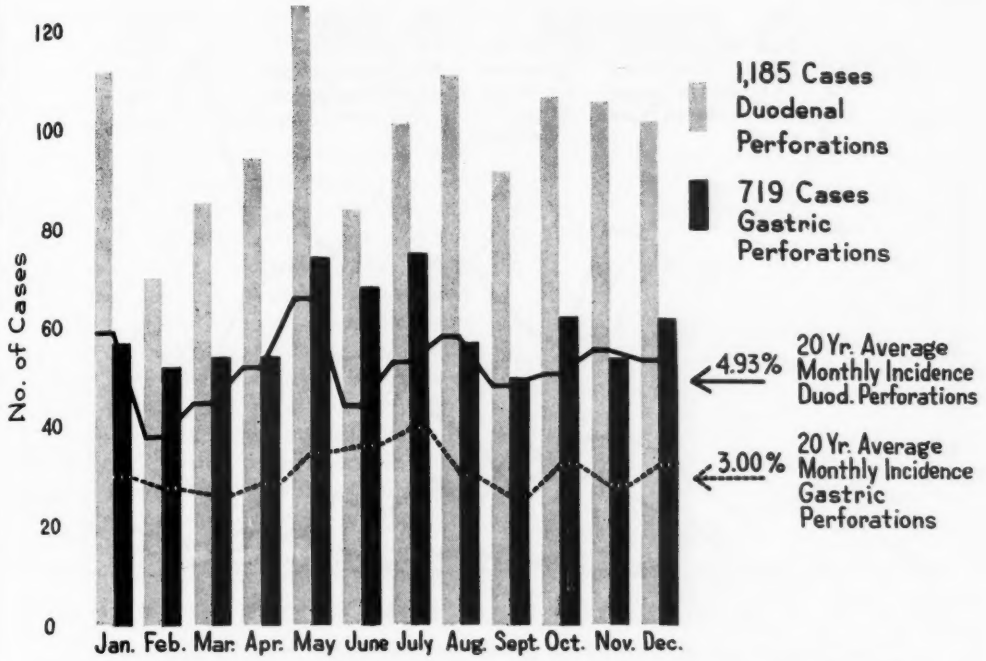

FIG. 6. Influence of month of admission upon incidence of gastroduodenal perforations. Although the incidence of duodenal perforation was always greater than gastric perforation in any month of the year, no seasonal trend could be established. The vertical bars indicate the total number of cases seen in that month for 20 years; the 2 curves indicate the 20 year averages expressed as percentages of the total number of cases. There is no parallel or reciprocal relationship.

The white collar group constituted 3.8 per cent of all perforations and 2.1 per cent of admissions; these were clerks, bookkeepers, musicians, technicians, salesmen, stenographers, and hospital personnel. The incidence of duodenal perforations was again greater; the mortality rate for the duodenal perforation was slightly less.

There were only 16 representatives of the professional group. These were artists, accountants, a pharmacist, a chiropodist, 3 college professors, 1 lawyer, 1 doctor, and 2 engineers. Thirteen of these had duodenal perforations from which 2 patients died. One of the 3 patients with gastric perforation died.

Family medical history. The most frequently listed diagnoses were pneumonia and heart disease. The mortality rate for all patients with peptic perforations and a family history of pneumonia was 22.4 per cent; it was 43 per cent for patients with a family history of heart disease. A family history of peptic ulcer was identified in 1.4 per cent. The only other diagnosis of significance in the family history was carcinoma; although an incidence of 1.5 per cent for all perforations is not excessive, a mortality rate of approximately 50 per cent for perforations was found among their progeny.

Past medical history. The most frequently recorded diagnosis was venereal disease (20.3 per cent), approximately 72 per cent gonorrhea, the remainder, syphilis. The mortality rate for perforation for this group was not remarkable.

The incidence of a positive ulcer history for all perforations was 19.1 per cent. If it is assumed that gastrointestinal bleeding of unknown cause is due to peptic ulcer, then

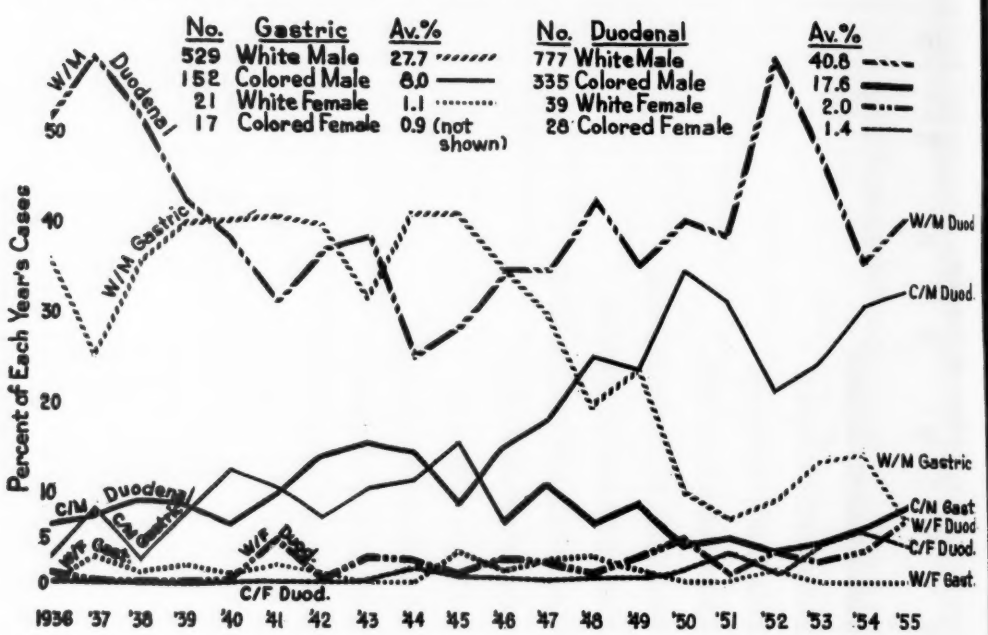

FIG. 7. The 20 year distribution of acute gastroduodenal perforations among the sexes of the white and colored races. The white male always had an incidence of perforations in excess of his hospital census; in the case of duodenal perforation he vacillated, but with gastric perforation there was a progressive decline since 1945. The incidence of perforation in the colored male exceeded his admission census only in recent years, due to a striking increase in duodenal perforations. Females of both races indicated a slight increase in duodenal perforations in recent years.

the incidence of a positive ulcer background would be 20.5 per cent. The mortality rate for perforation of patients with an ulcer history was average.

The next most frequent diagnosis was alcoholism, acute and chronic. Although this was recorded in the past history of 6.8 per cent of the patients with perforation, the diagnosis was made more often in the present admission; the mortality rate in these patients with a history of alcoholism was 35 per cent. Pneumonia was listed in the history of 5.4 per cent of these patients with only a slight influence on the mortality rate. A history of an acute infectious disease was recorded in 5.1 per cent of all patients, with a fatal outcome in over one-third. The incidence of heart disease was 2.3 per cent for both groups; the mortality rate was 50 per cent. Although the number of instances of asthma, carcinoma, hepatobiliary disease, diabetes, and cerebrovascular diseases in the past history were relatively few, the mortality rates for these were significantly in excess of the general average.

Past surgical history. The most frequent surgical procedure prior to perforation was an appendectomy, with an average mortality rate for a perforation of the ulcer. A previous closure of a perforated peptic ulcer was noted in 4.7 per cent of the patients with an 18.7 per cent mortality. Patients having had other operations for peptic ulcer were noted to have higher than average mortality. Patients with previous fractures and genitourinary operations showed a higher than average mortality.

Dietary habits. Only isolated instances of diets deficient in milk, meat, fats, or vitamins or combinations thereof were found in

the patient's history. A total of 14 patients followed an ulcer diet prior to perforation; 2 of these died. Forty-three patients did not follow an ulcer diet; the perforation proved fatal in 20.8 per cent of these.

The use of some form of alcoholic beverage in moderate or excessive quantities was acknowledged in the histories of 36.3 per cent of all patients with peptic perforations. Classifying the alcoholic intake either as whiskey, beer, or wine, a remarkable similarity in incidence was noted between gastric and duodenal perforations, although the mortality rate for the gastric was greater than for the duodenal. The mortality rates as a whole were less than average, with the exception of gastric perforations in wine drinkers. There was no significant difference between the mortality rates of moderate or heavy drinkers.

The frequency of the use of tobacco in moderate or excessive amounts was 27.1 per cent of all perforations. Although the mortality rate for the smoker with the gastric ulcer perforation exceeded that of the patient with duodenal perforation, it was not in excess of the norm in either group of patients studied.

Weight changes. Data as to weight changes were available on 397 patients or 21 per cent of all those with perforations. In 108 patients the weight was stated as constant; the mortality rate was 15.7 per cent, which is considerably less than the 24 per cent overall figure. In the remaining 289 patients who lost 5 or more pounds prior to perforation, the mortality rate was 36.0 per cent. In patients who lost 35 or more known pounds or in whom the weight loss was large but unknown in amount, the mortality rate was 50 per cent or higher.

In general, the incidence of weight loss prior to perforation was somewhat more frequent in gastric than in duodenal perforation (Fig. 9). The mortality rate for the patients with gastric perforations who lost 5 pounds or more was 41.8 per cent, whereas for those in the duodenal group it was 32.5 per cent.

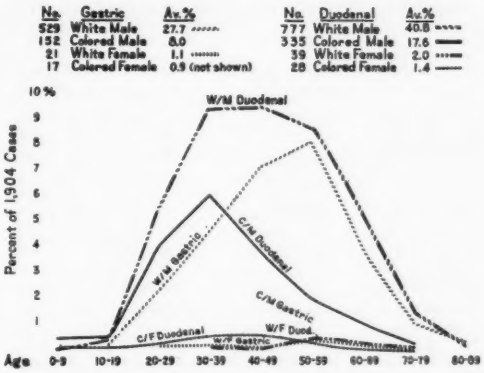

FIG. 8. Racial trend in each decade of gastroduodenal perforations. The peak decade for duodenal perforation in the white male came earlier than gastric perforation, whereas in the colored male it occurred in the same decade.

DISCUSSION

This is probably the largest series of acutely perforated peptic ulcers reported upon from a single institution. A frequency of perforation of 22.5 per cent for all patients with ulcers is higher than other reported series. DeBakey reported a 13.2 per cent incidence of perforations in a worldwide collection of 33,439 ulcer cases and an 8.09 per cent incidence among 2,607 ulcer cases studied by him from the Charity Hospital of New Orleans. Thompson found that perforations developed in 19.6 per cent of all ulcer patients admitted to the Los Angeles County Hospital. DeBakey noted a higher rise in the occurrence of acute perforations than ulcerations in general. In 1938, Portis and Jaffe reported the occurrence rate of perforation at the Cook County Hospital to be 14 per cent of all ulcer patients.

Because only objective criteria were accepted in screening the records, and since it is easier to obtain these for perforated ulcer than for other ulcer complications, it is possible that the incidence is weighted in favor of perforation. Data in the literature relative to the occurrence of perforation in ulcer patients varies considerably, depending upon whether it is reported from the author's individual practice or a large char-

TABLE VI.—COLLECTED SERIES COMPARING THE INCIDENCE AND MORTALITY OF GASTRIC AND DUODENAL PERFORATIONS

Author	*Type hospital*	*Year*	*No. of cases*	*Per cent gastric perforations*	*Per cent duodenal perforations*	*Per cent unknown*	*Per cent mortality gastroduodenal*	*Per cent mortality gastric*	*Per cent mortality duodenal*
Baritell, A. L.	Private	1946	88	19.3	80.7	—	1.1	—	—
Ingram, I. N.	Private	1927–1947	132	30.1	69.9	—	15.4	24.5	11.6
Kingsbury, H. A.	Private	1944–1949	170	11.7	86.4	1.9	10.0	—	—
Hamilton, E. C.	Veterans	1946–1952	72	4.1	95.9	—	1.5	—	—
Seeley, S. F.	Veterans	1945–1953	139	3.5	96.5	—	5.0	—	—
Mann, L. S.	Veterans	1956	157	15.7	83.4	—	—	—	—
McCaughan, J. J.	Veterans	1946–1956	277	17.0	82.3	—	3.2	—	—
Palumbo, L. T.	Veterans	1946–1956	93	21.5	78.5	—	—	—	—
DeBakey, M	Charity	1929–1938	211	47.6	52.3	—	18.7	—	—
DeBakey, M.	Charity	1929–1938	11,305	48.7	51.2	—	25.2	33.3	21.1
Donhauser, J. L.	Charity	1935–1951	146	50.0	50.0	—	23.5	—	—
Luer, C. A.	Charity	1938–1948	362	33.4	63.3	—	28.2	24.1	16.4
McElhinney, W. T.	Charity	1935–1946	336	34.5	56.8	8.6	20.2	—	—
Moore, S. W.	Charity	1928–1945	101	83.2	16.8	—	18.0	19.0	12.0
Mikal, S.	Charity	1938–1950	500	43.2	45.4	11.4	17.2	—	—
Miller, E. M.	Charity	1930–1951	193	36.9	63.1	—	27.6	—	—
Olson, H. B.	Charity	1938–1944	166	26.6	61.4	12.0	27.6	29.5	28.4
Schmitz, E. J.	Charity	1948–1952	136	25.0	68.3	6.7	24.5	41.2	18.6
Turner, F. P.	Charity	1929–1948	224	26.5	69.7	—	23.6	—	—
Present report	Charity	1936–1955	1,904	37.8	62.2	—	24.0	27.4	22.1

ity hospital. Thus, reporting upon a group of private practice patients, Emery and Monroe reported the incidence of perforation to be 7.7 per cent; Flood, 3.4 per cent; and Hurst and Stewart, 3.0 per cent.

The total of 1,904 perforations of an accepted group of 8,451 ulcer patients occurred in a hospital population of 1,372,117. This makes the incidence of ulcer 615 cases per 100,000 and of perforation 138 per 100,000. DeBakey's collected series for an earlier period had comparable data of 685 per 100,000 and 87 per 100,000. The incidence of perforation at Los Angeles County Hospital was 167 per 100,000 according to Thompson. The number of perforations per year abruptly increased during the years 1938 through 1940 and again during 1949 and 1950. Similar fluctuations were seen with bleeding ulcers, and at first glance would be attributed to the tension of war as was described by Spicer and associates as occurring during the blitzkrieg in England. However, this increase did not parallel the entry of the United States forces into the war, and it did not persist as long as the war did. It did not affect those of military age; there was no malnutrition; and whereas the first increase was in the incidence of gastric perforation, the second one was in duodenal perforation. On checking annual admissions from 1936 through 1955, an abrupt 5 to 6 per cent increase was noted in 1938, 1939, and 1940 with a subsequent decline. This was not the case in 1949 and 1950.

The incidence of 1,185 duodenal ulcer perforations and 719 gastric ulcer perforations is a ratio of approximately 8:5. McNealy and Howser reported 700 perforations from the Cook County Hospital between 1925 and 1938, of which 50.5 per cent were duodenal and 49.5 per cent were gastric. Portis and Jaffe reviewed the autopsy material of the same hospital for the years 1929 through 1936 and found 188 duodenal and 152 gastric perforations, a ratio of 1.2:1. The present study suggests a significant increase in the occurrence of duodenal perforations and a decrease in gastric perforations. Although this ratio of 8:5 declines with advancing decades, it was always in favor of duodenal perforation.

Gastric ulcer made up 29.8 per cent or 2,529 cases of all the peptic ulcer cases analyzed, duodenal ulcers accounting for 70.2 per cent (5,922 cases). The number of gastric ulcers which perforated was 719 or 28.4 per cent of the total number. The number of duodenal perforations, 1,185, accounted for

20.0 per cent of all duodenal ulcers. This would seem to indicate that the gastric ulcer has a greater proclivity for perforation than the duodenal, even though the total number of gastric perforations actually declined. Ivy and associates commented that, from their review of the literature, duodenal ulcer was more prone to perforate; this study does not support that opinion.

In addition, the ratio depends upon the type of institution from which the clinical material is collected. The predominantly private and veterans hospitals report indices of duodenal perforations 3 or more times as large as gastric (Table VI). Charity hospitals, however, report indices of gastric ulcer perforations which were much higher, almost equaling duodenal ulcer perforations.

An incidence of 2.3 per cent of perforations occurring on the posterior wall of the stomach or duodenum agrees with a 2.0 per cent incidence at the Charity Hospital of New Orleans, or 2.16 per cent quoted by DeBakey.

This and collected data indicate a decline in the incidence of gastric ulcer perforation. Prior to 1950 there occurred an average of 36 gastric perforations per year; since then, the average was 16 per year. At the same time the relative incidence of duodenal ulcer perforation had risen. These possible explanations can be offered: Europeans, as Alsted and DeBakey have observed, have a higher than average incidence of gastric ulcer. There has been less migration of Europeans in the past decade. There has been a much greater influx of the southern Negro, who seems to be predisposed to duodenal ulcer and perforation. Finally, a more aggressive surgical treatment of gastric ulcer soon after diagnosis may have reduced the gastric ulcer population.

The mortality rate of patient with a perforated peptic ulcer also appears to be directly related to the type of hospital practice. The mortality rates at the 3 private hospitals cited in Table VI were 1.1 per cent, 10.0 per cent and 15.4 per cent with an average of 8.8 per cent. The 5 veterans hospitals

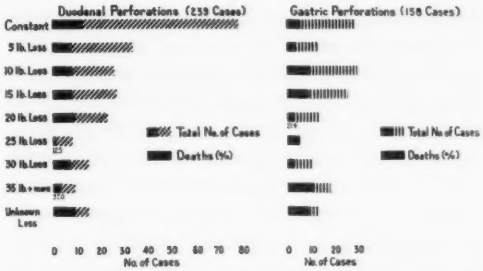

FIG. 9. Effect of weight loss on mortality rate. Patients whose weight was constant prior to perforation had lower than average mortality rates. Patients who lost 5 or more pounds in weight had a 36.0 per cent mortality rate; those who lost 35 or more pounds had mortality rates which rose as high as 69 per cent.

cited showed total mortality percentages between 0 and 5 with an average of 3.1 per cent. In the 11 charity hospitals cited in the United States, the average mortality rate was 23.3 per cent, the lowest was 17.2 per cent, and the highest 28.2 per cent. This series reports a 24.0 per cent over-all mortality.

All reports in the American literature are in agreement that gastric perforations carried a significantly higher mortality rate (Table VI). This was also true in the collected world-wide series of DeBakey which antecedes by 1 decade the 20 year period covered in this study. Although there was a rare year in which the trend might have reversed itself, the mortality rate of duodenal perforations at the Cook County Hospital for the years 1936 through 1955 averaged 5.3 per cent less than the gastric. In 5 institutions listed in Table VI, this difference was even greater.

It has been a practice in some institutional reports to remove from mortality rates those cases of perforations which were diagnosed only at autopsy. For example, among the 193 deaths tabulated as medical deaths from duodenal perforation, 48 were due to perforations unrecognized prior to necropsy. In a discussion of "conservative" treatment, one might dismiss these and reduce the medical mortality from 70.2 per cent to 45.0 per cent; similarly, 19 of 64

deaths from gastric perforations were unrecognizable prior to necropsy, with a resultant decline in medical mortality at the Cook County Hospital from 87.6 per cent to 59.0 per cent. In one report from a veterans hospital a total mortality rate of 5.0 per cent is never specifically stated, but a mortality rate of 1.5 per cent is given in support of a nonoperative method of treatment. This was done by Seeley and Campbell's assumption that only 2 patients of the 7 who died in a series of 135 patients were really suitable for this treatment. Taylor and Egbert emphasized the danger in this type of analysis. It is probably sufficient that the mortality rates of the conservatively treated patients recognized as having perforation ante mortem was 59 per cent for the gastric cases and 46 per cent for the duodenal; the adequacies and delays in treatment of these patients will be reviewed at a later date.

DeBakey stated that although he observed remarkable improvement in the treatment of patients with perforated peptic ulcer in his world-wide survey for the first 3 decades of this century, he was disappointed in the degree of improvement for the years 1929 through 1938. The second decade studied by us witnessed a significant total lowering of the mortality of patients with duodenal perforations but not of those with gastric perforations. The mortality rate of patients with duodenal perforations was 27.8 per cent prior to 1946; it fell to 17.7 per cent since then. At the Cincinnati General Hospital, McElhinney and Holzer noted a decline in the mortality of patients with perforated ulcer from 31.0 per cent in 1936 and 1937 to 11.7 per cent for the period of 1944 to 1946. Olson and Schmitz and their associates reported a decline in mortality rate for patients with duodenal perforations from 28.4 per cent for the years 1938 to 1944 to 18.6 per cent for the period 1948 to 1952. The mortality rate for patients with gastric perforations in the same two periods rose from 29.5 per cent to 41.2 per cent. Miller and associates compared the years 1930 to 1941 and 1942 to 1951 at the Metropolitan Hospital in New York and found that the general mortality rate declined from 25.2 per cent to 19.3 per cent. Comparing the mortality rates of different types of hospitals in different years can be misleading.

Much of the significance of the observations concerning age, sex, and race depends upon the population and the community from which patients are drawn. United States Census Bureau figures indicate that the most rapid growth in Chicago's population was in the nonwhite population. According to these data, 8.3 per cent of the city's residents or 282,244 were Negro in 1940. By November 1955, this group had increased to 633,000 or 16.7 per cent of the total.

The percentage of nonwhites admitted to the Cook County Hospital was 45.2 per cent at the onset and 57.2 per cent at the conclusion of this study. Therefore, the makeup of census of this hospital was tabulated by age in decades, sex, and race. This has been presented in Tables I, II and III, but further comment is necessary. Obstetric services averaged 30 per cent of total admissions; of these females, an average of 89 per cent were colored. Patients under 10 years of age accounted for 10 per cent of total admissions, of which an average of 81 per cent have been Negro. The urology and fracture services were attended dominantly by males advanced in years. All 4 of these services contributed relatively few cases to this series of perforated peptic ulcers. For these reasons the census was limited to patients on the adult male and female medical and surgical services.

While there has been a 10 per cent increase in the percentage of admissions of colored males in 20 years, the increase in the incidence of perforated duodenal ulcer in these males was 24 per cent. The total percentage of white males admitted has always exceeded the white females. In a breakdown of ages by decades, the admissions of white males always exceeded the females. The admissions of colored females exceeded the colored males who were between 10 and 29

years of age; thereafter, the colored male slightly outnumbered the colored female. Comparing the 2 races, particularly the males who constituted 94.5 per cent of the cases, the colored males who were under 50 years of age outnumbered the white males; after age 50, the reverse was true.

One hundred and five or 5.5 per cent of 1,904 peptic perforations occurred in the female. This can be compared to an incidence of 3.8 per cent reported by McElhinney and Holzer from the Cincinnati General Hospital, of 1.9 per cent reported by DeBakey from the Charity Hospital of New Orleans, of 4.7 per cent reported by Luer from the St. Louis City Hospital, and of 7.7 per cent in DeBakey's collected series.

Some reports note a rising incidence of perforating ulcers in females in recent years as evidenced by figures of 10 per cent reported by Moore and Hendricks from the ward services of the Presbyterian Hospital in New York and 13.2 per cent reported by Schmitz and associates from the King County Hospital in Seattle. There is a suggestion of this in the data for duodenal perforations in this series. As expected, the veterans hospitals report few, if any, females with perforation. Prior to 1900, most references stated that the incidence in the female was as great as in the male, if not greater. Ivy and co-workers collected 13 references between 1857 and 1941 showing a progressive decrease in the percentage of perforations in the female from 65 per cent to 7 per cent. However, Sandweiss and associates in 1939 found only 1 proved case of active peptic ulcer in 70,310 consecutive hospital admissions of pregnant women during a period of 10 years.

Cook County Hospital census figures for the adult male and female classified as to white and colored showed that white males accounted for between 42.2 per cent and 28.4 per cent of admissions; colored males for between 19.5 per cent and 29.5 per cent; white females for between 20.9 per cent and 13.8 per cent; and colored females between 15.7 per cent and 28.2 per cent. The aforementioned figures refer to the beginning and end of the study, respectively. The distribution of perforations was 68.5 per cent for the white male, 25.6 per cent for the colored male, 3.1 per cent for the white female, and 2.4 per cent for the colored female. The disparities are obvious. The white male showed an incidence of perforation 20 times greater than in the white female and 2½ times that of the colored male. The incidence of perforation was 10 times greater in the colored male than in the colored female. In females, the incidence for perforation in both races was practically the same. DeBakey's own figures for perforation were 60.6 per cent in white and 39.3 per cent in colored patients. He collected references from the world literature indicating that the incidence of perforation in the colored individual varied from rare to 25.0 per cent. Perforation is reputed to be exceedingly low in the primitive Negro living in Africa.

In the white male the mortality rate was virtually twice that in the colored male for both gastric and duodenal perforation but one-half the mortality rate of that in the white female. The colored female had 3 times the mortality rate of the colored male and an only slightly lower mortality than the white female. Difficulty in recognizing a perforation in the female may be indicated by the fact that 42.5 per cent of the females were treated conservatively and died. The incidence of conservatively treated perforations for both sexes was 14.0 per cent. The absence of Negro patients past the age of 79 explains only part of the reason for the improved mortality in this race. If this racial difference was significant, the Negro female should not have fared almost as poorly as the white female. In veterans hospitals the absence of the female may explain, in part, the lower mortality rates seen. Luer found the mortality rate to be 47 per cent for the female. DeBakey found this mortality figure to be 43.9 per cent in his literary review.

The distribution in age decades between

different reports was then compared by arranging available data according to the type of institution: viz., veterans, private, or charity services (Table VII). DeBakey reported only 5 pediatric perforations in his collected series of 16,752 perforations from a world-wide survey and none from the Charity Hospital of New Orleans, as compared to 10 reported by the Cook County Hospital. Reports of all series of perforation in infancy emphasize almost 100 per cent mortality. This, too, is of significance in analyzing the data of veterans and private hospitals, since no instances of perforation in infancy are cited. The veterans hospitals reported that the largest number of their patients were between 20 and 29 years old. All types of institutions reported approximately the same percentage of patients for the age decade of 30 to 39 years. For the 40 to 49 year old patients, the veterans hospitals showed a lower incidence of cases. The incidence for 50 to 59 year old patients was again slightly lower in the veteran installations. For patients in the decades beyond 60 years of age, the private and veterans hospitals had a significantly lower incidence than did charity hospitals. All patients beyond the age of 80 were reported from charity services. Although an age distribution younger than the general population could be anticipated for a veterans hospital, it does not necessarily apply to private hospitals. Hospitalization insurance may afford an answer, for medical indigency increases with age.

Except for the first decade of life, mortality rates show a progressive increase with each decade, the rise being least in the veterans series, next in the private series, and the most rapid in the charity hospital series (Table VII). The fact that mortality rates are uniformly lower for veteran and private patients than for charity patients, at the same level, indicates that other factors than age alone must therefore be taken into account.

Confusion exists as to a seasonal predisposition for perforation. The differences by months or seasons were not significant and were not consistent for either type of perforation, nor was there a better correlation of mortality rates. DeBakey, in his collective review of world literature prior to 1938, found 4 references which stated that the incidence was higher in the spring and fall; 2 references favored an increased incidence in autumn and winter, and 1 in summer. When he added 2,324 cases together, spring appeared to be the peak season. His own experience suggested the fall, but he ventured an opinion that the difference was probably not significant. Luer reported the incidence to be the highest and the mortality rate lowest in the spring.

The marked difference in mortality in favor of the Negro might conceivably be explained by the fact that colored males less than 40 years old accounted for a disproportionately larger percentage of both duodenal and gastric perforations. However, at any specified age decade the mortality rate of the Negro race was usually significantly lower than the mortality rate of the white race (Table III). The disproportionately higher mortality rate for both types of ulcer perforations in the European could not be explained on the basis of language difficulties, for the same trend was apparent in English-speaking Europeans.

In a hospital census in which 65 per cent were classified as dependents the incidence of perforation was 12.9 per cent. The nonskilled laborers exceeded the incidence of perforation of those semiskilled; the latter in turn outnumbered the skilled laborer; all 3 of these groups accounted for 30 per cent of the census and 53.4 per cent of the perforations, 36.5 per cent duodenal and 16.9 per cent gastric. It may be concluded that a relatively higher incidence of perforations occurred among laborers than dependents. Even allowing for approximately one-fifth of the dependents being females or children, the relative incidence of occurrence of perforation in this dependent class is low. However, the reverse is true of the mortality rate, and again we must appreciate the mor-

TABLE VII.—COLLECTED SERIES COMPARING THE INCIDENCE AND MORTALITY OF PERFORATED PEPTIC ULCERS ACCORDING TO AGE DECADE

	—(Cook County Hospital)—					
Age decade, yrs.	*Per cent* hospital census*	*Present report*	*World-wide series*	*United States, private hospitals*	*United States, veterans hospitals*	*United States, charity hospitals*
0 to 9						
No. of cases	**	10	5	—	—	1
Per cent of cases		0.5	0.07	—	—	0.6
Per cent mortality		90.0	100.0	—	—	100.0
10 to 19						
No. of cases	6.5– 5.5	17	190	2	4	20
Per cent of cases		0.9	4.7	0.5	0.7	1.3
Per cent mortality		0	12.2	0	0	5.0
20 to 29						
No. of cases	11.4–13.9	255	1,019	45	157	175
Per cent of cases		13.4	24.5	11.7	31.0	11.8
Per cent mortality		5.7	12.2	0	0	8.5
30 to 39						
No. of cases	13.7– 5.4	460	1,112	92	146	324
Per cent of cases		24.1	27.1	24.0	28.8	21.7
Per cent mortality		11.2	18.9	4.3	0.6	7.1
40 to 49						
No. of cases	16.6–15.8	457	906	113	58	377
Per cent of cases		23.9	21.8	29.4	11.5	25.3
Per cent mortality		19.9	28.0	5.3	5.1	15.6
50 to 59						
No. of cases	19.4–16.3	400	606	94	93	318
Per cent of cases		21.0	14.6	24.5	18.3	21.2
Per cent mortality		32.2	40.8	18.1	4.3	29.8
60 to 69						
No. of cases	16.5–15.3	213	244	26	44	185
Per cent of cases		11.2	5.9	6.7	8.7	12.5
Per cent mortality		48.4	55.3	23.1	15.9	32.4
70 to 79						
No. of cases	9.2–11.7	72	65	11	4	73
Per cent of cases		3.7	1.5	2.8	0.7	4.8
Per cent mortality		61.0	53.8	45.4	25.0	59.0
80 to 89						
No. of cases	2.1– 3.7	20	—	—	—	15
Per cent of cases		1.0	—	—	—	1.0
Per cent mortality		75.0	—	—	—	80.0
Total No. of cases		1,904	4,147	383	506	1,488
Average mortality, per cent		24.0	25.2	9.9	3.1	23.3

*Listed as percentages at the beginning and end of the study, respectively.
**Not calculated because these 10 cases occurred in approximately 150,000 pediatric admissions.

tality rates of the extremes in age and of the females for the interpretation. DeBakey has reviewed this phase of the problem in the literature and indicates that laborers, as a class, dominate in the incidence of perforation. The percentages varied from 50 to 75; his own series was 72.9 per cent. Tidy, in reporting 1,580 gastric and 1,025 duodenal ulcers from St. Thomas' Hospital, London, indicated that gastric ulcers occurred more frequently in skilled and unskilled manual laborers and duodenal ulcers more frequently in professional people. Cook County Hospital data do not include sufficient numbers of professional people for comparison, but even in our laborers the incidence of perforations, at least, was in favor of duodenal ulcer.

In analyzing the cause for an "alarming" increase in the rise of peptic ulcer perforations, DeBakey cited several references incriminating alcohol and tobacco. The data submitted in this series do not confirm this. The admitted use of alcoholic beverages in 36 per cent of this series of patients is not high; at the King County Hospital in

Seattle, Olson and Norgore observed the incidence of alcoholism to be 22.4 per cent in a 1938 to 1944 period. This figure rose to 47 per cent at the same hospital during a 1948 to 1952 period, according to Schmitz and co-workers. Walker in 1915 claimed that two-thirds of his 78 patients drank prior to perforation. Wolff found this to be true in four-fifths of 55 cases in 1929. Slightly more than one-fourth of the patients in this report acknowledged the use of tobacco in moderate or excessive amounts but without a noticeable effect on the mortality rate from perforation.

SUMMARY

1. Perforation accounted for 22.5 per cent of all admissions for ulcer and 138 per 100,000 hospital admissions during 1936 through 1955.

2. There were 719 gastric perforations, 37.7 per cent, and 1,185 duodenal perforations, 62.2 per cent. There was a relative increase of duodenal perforations and a decrease of gastric perforations in the second decade studied.

3. The total mortality rate was 24.0 per cent. For gastric perforation it averaged 27.5 per cent and for duodenal perforations, 22.1 per cent. The surgical mortality rate for gastric ulcer perforation was 20.2 per cent and for duodenal perforation it was 12.4 per cent; the lowered mortality in the second decade for duodenal perforation was significant, but the death rate remained unchanged for gastric perforation.

4. The mortality rate for 10.1 per cent of the gastric perforations conservatively treated or unrecognized until autopsy was 87.6 per cent. The mortality rate for the 16.3 per cent of duodenal perforations similarly treated was 70.2 per cent.

5. As the perforation site moved from the duodenal bulb to the cardia of the stomach, the mortality rate increased.

6. The mortality rate was 0 for patients aged 10 to 19 years and rose progressively with each decade to 75.0 per cent for patients aged 80 to 89 years. In the first decade of life, the mortality rate was 90 per cent; all of these patients were less than 6 months of age.

7. Ninety-four and six-tenths per cent of peptic perforations occurred in the male; the remaining 5.4 per cent were in the female. The white male accounted for 68.7 per cent of the perforations, the colored male for 25.6 per cent; the white female accounted for 3.1 per cent and the colored female for 2.3 per cent. The occurrence of peptic ulcer perforation in the white male is out of all proportion to the ratio of admittance.

8. The mortality rate for perforation in the female, 53.3 per cent, is virtually 2½ times that of the male, 22.3 per cent; the mortality rate of the white male, 25.7 per cent, is virtually twice that of the colored male, 13.1 per cent.

9. The white male between the ages of 20 through 59 years showed a frequency of perforation of an ulcer out of proportion to the frequency of his hospital admission. The colored male showed this only for the ages of 30 through 39 years, by a narrow margin.

10. A predominance of duodenal perforation in our patients of southern extraction was noted, as was a predisposition for gastric perforation in patients of European extraction. The mortality rates for the European was significantly higher in both types of perforations.

11. A predominance of perforations was seen in laborers; their hospital census was 30 per cent and their perforation incidence was 53.4 per cent.

12. A positive antecedent diagnosis of a peptic ulcer was obtained in only 19.1 per cent of patients. A surgical closure of a previous perforation was reported in 4.7 per cent of these cases.

13. The use of alcoholic beverages or tobacco did not appear to influence the incidence or prognosis of peptic perforation.

14. Weight loss prior to perforation affected the prognosis of both types of perforation adversely and in proportion to its degree.

15. The consistently lower mortality rates of peptic perforation as reported by veteran and private hospital series can be attributed to a concentration of patients in the median age groups, the relative infrequency of gastric perforations, and the lack of females with perforation. As a result of further study of symptoms, physical findings, laboratory data, and operative experience, other additional factors of significance may evolve.

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REGIONAL JEJUNITIS

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REGIONAL JEJUNITIS is that variety of regional enteritis in which the initial manifestations are mainly or exclusively in the jejunum. Regional jejunitis has a clinical and roentgenographic pattern different from that encountered when the disease is localized to the ileum. For this reason, it seems important to describe the pathologic, clinical, and roentgenologic findings in 22 cases in which granulomatous enteritis was confined originally to the jejunum. In terms of incidence, as known at present, regional jejunitis is not a problem of great magnitude, comprising about 1.9 per cent of all cases of regional enteritis. The most common site of granulomatous involvement is the distal portion of the ileum, and the frequency progressively diminishes in the more proximal portions of the gastrointestinal tract. Crohn and Yarnis, in their experience with 676 cases of regional enteritis, record 9 cases limited solely to the jejunum. Sixty-one involved both the ileum and jejunum; 606 involved the terminal portion of the ileum. It is of interest that only 4 cases affecting the duodenum and 2 involving the stomach were noted. Van Patter and associates recorded the jejunum to be the only site of disease in 11 of 315 operative cases (3.5 per cent).

Instances of isolated regional jejunitis have been documented in the literature and at least 36 such cases have been described. Practically all of these patients appeared to have long-standing disease. However, early cases of jejunitis are being recognized with increasing frequency. Many of these apparently proceed to the more chronic form. On the other hand, isolated instances of acute regional jejunitis have been reported which have healed completely without sequelae. In these instances, the diagnosis has arisen from observations made at laparotomy, not necessarily with pathologic or roentgenographic confirmation.

An acute form of necrotizing phlegmonous jejunitis characterized by early perforation and a high mortality has been reported in Europe. This form is in contrast to regional granulomatous jejunitis which follows a long, slowly progressive course.

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PATHOLOGY

Roentgenologically the prestenotic phase of the disease has been demonstrated on a number of occasions (Fig. 1). Some of these cases have been followed up until the actual development of stenosis. However, since none of our patients has been operated upon in the prestenotic period, the pathologic signs of that phase have not been observed. It would seem that this stage of the disease would be encountered when long segments of jejunum are resected for multiple areas of involvement. However, it has been our experience that such resected specimens show all the involved areas to be in the cicatrizing stenotic phase. This observation suggests that the disease appears in different segments at approximately the same time and progresses in them at the same rate.

The histopathologic appearance of regional jejunitis is essentially the same as that encountered in distal ileitis with stenosis. However, ulceration, perforation, and their sequelae are much less common in regional jejunitis than in ileitis. The mesentery also rarely demonstrates the degree of thickening seen in ileitis. On the other hand,

stenosis with obstruction is more common in jejunitis than in the distal forms of the disease.

The areas of involvement are much shorter in regional jejunitis than in ileitis (Fig. 3b). Long, continuous, segmental involvement which in distal ileitis may extend for 3 or 4 feet is not encountered as a rule. Diseased segments longer than 6 to 12 inches are uncommon. Most are even shorter and are frequently annular. When a single stenotic lesion is present, there is continuous dilatation of the proximal bowel. However, more commonly, multiple stenotic segments are encountered. In such instances, loops of normal bowel are obstructed both distally and proximally. Since the contents of the obstructed segments are prevented from passing distally or proximally, an extraordinary degree of distention of the doubly obstructed loop occurs (Fig. 4a). This obstruction tapers off in either direction, being most marked in the center. The term "hammock type" distention has been utilized to describe this appearance. When multiple alternating short segments of constriction and dilatation occur, a pattern described as a "sausage link" appearance is produced. Stercoral or tension ulcers may be demonstrated in the chronically obstructed loops.

An important pathologic finding which deserves emphasis is the occurrence of malignant degeneration in the stenosing type of regional jejunitis (Fig. 7). Whereas carcinoma has been observed only once in hundreds of cases of distal ileitis, a highly malignant form of adenocarcinoma developed in 1 of 22 patients observed in this series (2). We have seen another case of carcinoma developing in an area of regional jejunitis. This case has not been included because the terminal ileum was also involved.

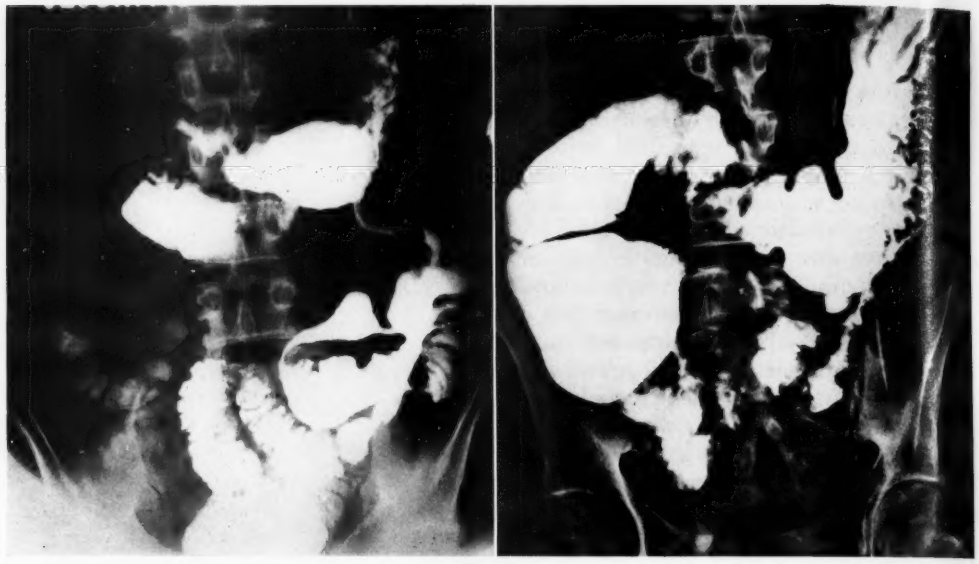
CLINICAL FEATURES

Most of the patients were relatively youthful. Their ages ranged from 18 to 42 years; the majority were in their second or third decade. In the present group, as well as in the reported cases of Crohn and Van Patter and their associates, the preponderance of males has been characteristic.

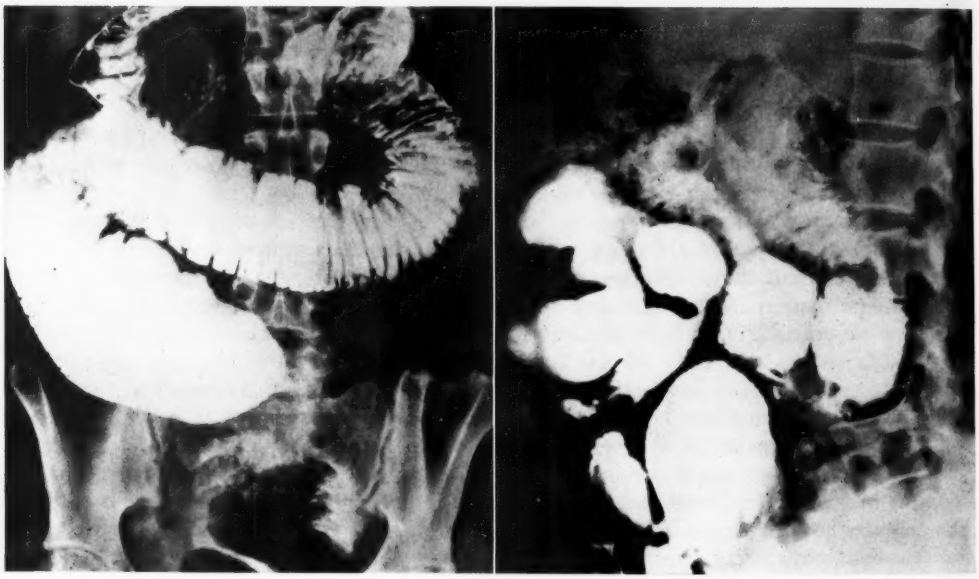
FIG. 1. There is thickening and blunting of the folds associated with numerous small nodules. Irregularity of the contours, some rigidity and straightening of the loops as well as increased secretions are noted. Nonstenotic phase of jejunitis.

In the prestenotic phase of the disease, the clinical symptoms are remarkable in their paucity. On close questioning, a history may be elicited of transient episodes of diarrhea preceding the onset of major abdominal symptoms by many years. Because of this vague symptomatology, it is difficult to state with any degree of certainty the duration of regional jejunitis before it is recognized. This early relatively benign course of the disease may be due to the fact that severe mucosal ulcerations with perforation and secondary bacterial infection are not as prominent a feature as in distal ileitis.

In some patients, as the disease progresses, symptoms of sufficient severity may develop to warrant further study. These symptoms are mainly fever, abdominal dis-



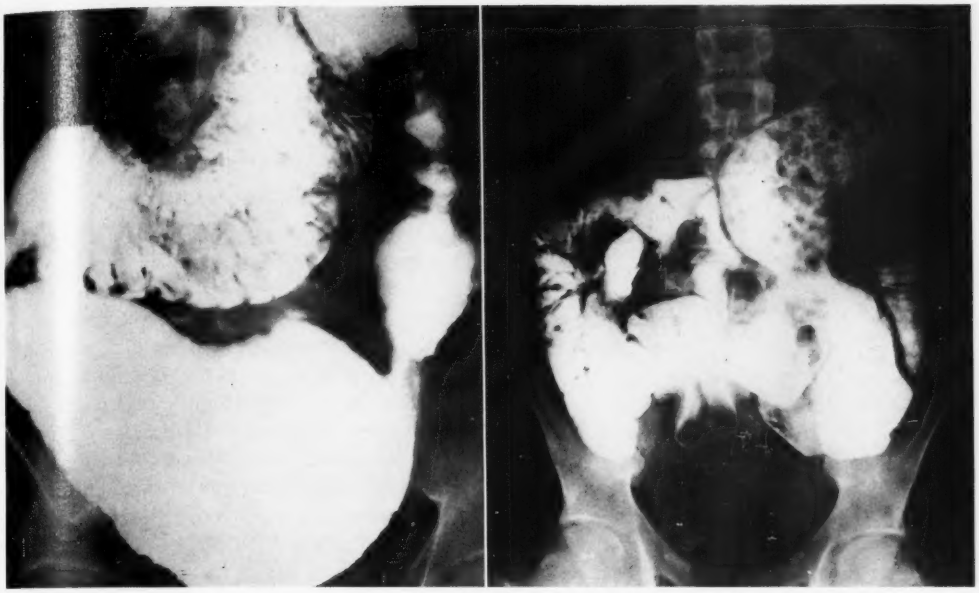
a FIG. 2. b



a FIG. 3. b

FIG. 2. a, Starting at the ligament of Treitz, alternating areas of constriction and dilatation of the upper jejunum are seen. The duodenum is dilated. There is marked rigidity and uncoiling of the bowel loops with effacement of the mucosal folds. b, There is marked dilatation of second and third portions of duodenum secondary to stenosing jejunitis of proximal jejunum.

FIG. 3. a, There is a short constricted segment demonstrated with marked dilatation of the proximal portion of the jejunum. Despite the marked narrowing, examination the following day revealed the fact that the barium was present in the colon. b, Characteristic alternating areas of stenosis and dilatation are best seen on the lateral projection.



a FIG. 4. b

FIG. 4. a, There is a hugely dilated loop of jejunum enclosed by two short strictured segments. Additional narrowed segments are also identified. b, There is considerable dilatation of the middle and distal portions of the jejunum which contain retained secretions and food particles. The site of stricture is not visualized on this film.

comfort, pain, and moderate diarrhea. In such cases, roentgenographic study may disclose nonstenosing jejunitis. With the onset of the stenotic phase, weight loss, abdominal distress, pain, vomiting, and distention may develop. It is surprising that even with marked roentgenographic evidence of obstruction, these patients may be fairly comfortable. Transient attacks of acute, apparently complete, intestinal obstruction with obstipation and vomiting may occur. In our experience, it has never been necessary to operate for acute intestinal obstruction. Relief has been obtained by stopping all intake, administering fluids and electrolytes intravenously, and maintaining continuous suction through a long intestinal tube. In many cases, even nasogastric suction has proved effective in relieving the obstruction.

Not infrequently the systemic effects of the malnutrition associated with this high obstruction dominate the picture. Loss of weight may be extreme. Low grade fever is often encountered. Clubbing of the fingers has been noted on occasion. Complications such as abscesses and fistula formation, arthritis, and skin lesions are not as frequent as in the more distal forms.

ROENTGENOGRAPHIC FINDINGS

In distal ileitis the roentgenographic picture is dominated by the appearance of diseased segments of bowel. In regional jejunitis, on the other hand, the sequelae of the diseased stenotic segments, namely, markedly dilated, chronically obstructed loops, are the striking finding (Fig. 4a and b). The retention of food and secretions and the inflammatory reaction which frequently develops in these chronically obstructed loops produce roentgenographic features which are characteristic of prolonged obstruction. It is often impossible in this situation to determine roentgenologically whether there is intrinsic

FIG. 5. Stenosing jejunitis.

involvement or whether changes are produced by the longstanding obstruction. The diameter of the doubly obstructed loops may attain the proportions of a markedly distended colon.

In most cases, the stenotic segments are easily visualized (Fig. 3a and b). However, when numerous overlapping dilated intestinal loops are present, a single, short stricture may be difficult to delineate (Fig. 4b). Although the stenotic segments indicate a considerable degree of fibrosis, the narrowing may be further enhanced by superimposed edema and spasm resulting from the inflammation. The contours of the narrowed segments generally are smooth. The lumen is concentrically located. The mucosa may be castlike or reveal numerous pseudopolyps and ulcerations. The stenotic segments are rigid. They may be single or multiple and vary considerably in length (Fig. 2a and b). If there is only a single area of constriction, a more or less uniform dilatation of the proximal bowel may be seen. The presence of skip lesions may result in a "hammock type" or "sausage link" type of deformity (Fig. 3b). When obstruction occurs near the fossa of Treitz, duodenal and even gastric dilatation may be evident (Fig. 2a and b).

Fistulas, abscess formation, and sinus tracts are rarely noted. In one instance in which an external fistula developed after the drainage of an abscess, the internal site of origin was in a dilated loop not involved by intrinsic inflammatory disease. It is likely that it resulted from the perforation of a tension ulcer.

One of us has had the opportunity of following up for a period of 16 years 25 cases of regional enteritis in which stenosis eventually developed. The shortest roentgenologically recognizable interval between the onset of disease and the development of stenosis was 4 years (Figs. 5 and 6a and b); the longest interval was 16 years. In many of these cases, healing of mucosal ulcerations occurred, but a return to a normal intestinal pattern was not observed.

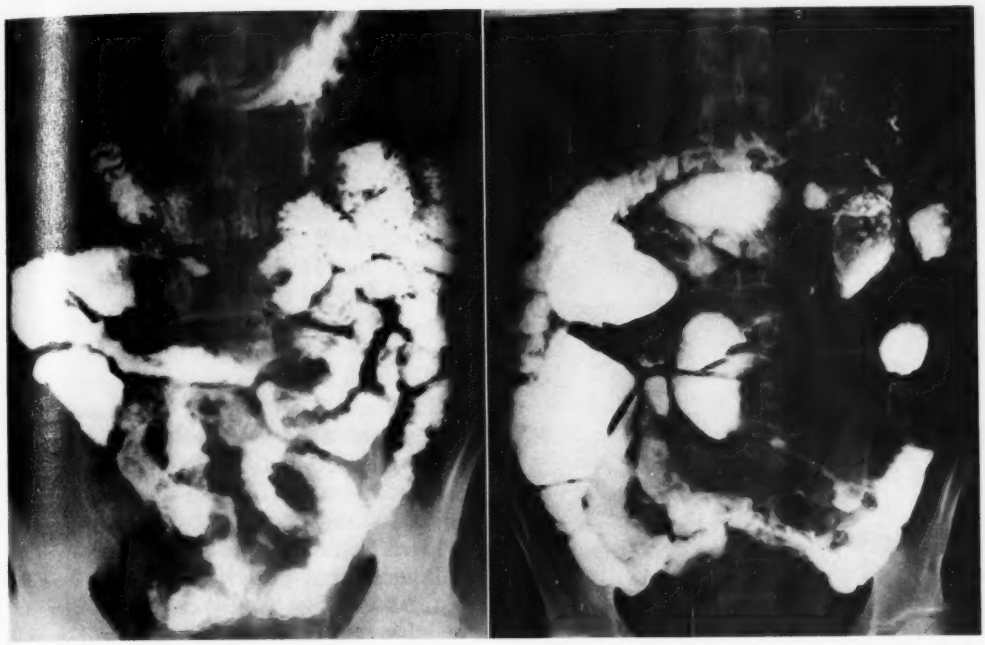
The roentgenographic characteristics of jejunitis, as in other forms of regional enteritis, are as a rule sufficiently distinctive so that diagnosis presents little difficulty. In an occasional case, Hodgkin's disease or lymphosarcoma may present an entirely similar appearance, especially to the nonstenosing phase of jejunitis. Differentiation may be impossible.

TREATMENT

In the treatment of distal regional enteritis, conservatism is becoming more and more the order of the day. In general, it can be said that operation is reserved for complications of the disease.

Similarly, in regional jejunitis it is our belief that operation before the onset of demonstrable obstruction is not indicated. There is usually only one reason for operation in regional jejunitis, i.e., the onset of obvious obstruction. This is especially the case when large dilated loops of bowel are present between multiple obstructions. Even if new areas of disease appear later in the more distal portion of the bowel, the general state of many of these patients is better.

As noted previously, episodes of acute intestinal obstruction will respond to continuous suction through either the long tube



a b

FIG. 6. a, Extension involving most of the small intestine approximately 1 year after resection. b, Stricture formation 4 years later.

or a Levin tube. Preoperative preparation, even in the case of nonacute obstruction, should be preceded by a few days of such suction in order to decompress the chronically obstructed loops, the appropriate fluid and electrolyte components being administered intravenously in the interim.

Regional jejunitis does not lend itself to bypass procedures with exclusion. Furthermore, there would be the danger of the multiple, obstructed segments eventually becoming distended by their own secretions as the bypassed stenotic zones went on to further fibrosis. Enteroanastomosis in continuity to bypass the diseased segments would in all likelihood be ineffective. Resection of the diseased segments and the intervening dilated bowel is the method of choice. In order to conserve bowel, the resection should be carried as close to the most proximally and most distally involved segment as possible.

In more proximal involvement near the duodenojejunal angle, a retrocolic duodenojejunostomy to the right of the middle colic artery should be performed. Dilatation and thickening of the retroperitoneal portion of the duodenum as the result of long-standing obstruction makes this procedure relatively simple. Gastroenterostomy should be employed only when involvement of the duodenum itself by inflammatory disease prevents an anastomosis at that site. The entire small intestine, as well as the colon, should be explored in every instance.

FOLLOW-UP EXAMINATION

Of the original 22 patients, we have lost contact with 8. Results of prolonged observation of the remaining 14 are available. Five have not undergone operation. Of these, 1 is not sufficiently obstructed to require intervention at the present time. Two have refused operation. Two others have

FIG. 7. Stenosing jejunitis starting at the ligament of Treitz and involving the proximal half of jejunum. At approximately 6 inches from the ligament of Treitz, carcinoma was identified in the narrowed area.

involvement of the entire jejunum beginning at the ligament of Treitz.

Nine were operated upon. Two had a duodenojejunostomy. One had a gastroenterostomy, later revised to a duodenojejunostomy with pyloroplasty. This patient had obstruction at the ligament of Treitz, and the initial procedure did not adequately circumvent the obstruction. An enteroenterostomy was performed in 1 patient; the site was subsequently resected with diseased jejunum because of continuing symptoms. In 5 patients, resection with primary anastomosis was performed.

One operative death after duodenojejunostomy performed elsewhere is recorded. Of the remaining 8 patients who underwent operation, new small intestinal disease developed in 5 within 6 months to 3 years after operation. Carcinoma of the jejunum in an area of jejunitis was resected in 1 patient. Local recurrence and hepatic metastases were demonstrated at operation 9 months later.

Despite the frequency of new disease after operation, most of these patients feel surprisingly well upon relief of their prolonged obstruction. However, 2 patients have progressed rapidly to stenosis and are manifesting obstructive symptoms again.

SUMMARY

Regional jejunitis is an uncommon form of granulomatous enteritis. Twenty-two cases are recorded. Pathologic involvement is localized usually to the proximal or midjejunum and is characterized by stenosis with single or multiple segments of alternate dilatation and constriction. Diarrhea and fistulas are less common and obstructive symptoms more common than in granulomatous disease involving other regions of the small bowel. The diagnosis is established by roentgenographic visualization of the dilated loops and stenotic segments pathognomonic of this disease. Treatment is usually symptomatic until prolonged obstruction supervenes. When surgical intervention becomes necessary, resection is the treatment of choice. Duodenojejunostomy is performed when there is obstruction at the ligament of Treitz. Extension of disease after operation is common, but the relief from symptoms may be remarkable.

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EDITORIALS

TISSUE TRANSPLANTATION

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THE CURE of illness by replacing diseased organs with healthy homografts is an intriguing possibility. So much attention is now focused on this subject in surgical research laboratories that organ restoration may be the next field of rapid surgical advance.

The immediate problems to be overcome are to induce the recipient of a homograft to accept the foreign tissue of the donor and to induce the transplant to accept the recipient.

There are two phases to the homograft rejection phenomenon. The first is an early nonspecific reaction characterized by local cellular infiltration at the site of the graft. The second is an antigen-antibody reaction which occurs after the grafted material has acted as an antigen and the recipient of the graft has had time to respond by the formation of specific antibodies.

Homograft rejection is a function of the lymphoid and reticuloendothelial systems and possibly also the bone marrow and plasma cell systems. Antibodies to homografts are humoral and cellular. The success of homografts in patients with agammaglobulinemia attests to the role of humoral antibodies in this reaction. The persistence of a viable homograft when a diffusion chamber is interposed between the graft and cellular elements of the host is an indication that lymphocytic elements are also important. Leucocytes may play a role in rendering the foreign protein of a donor tissue effective as an antigen, just as occurs with bacterial antigens, even though leucocytosis and suppuration are not a striking feature of homograft rejection unless infection is present.

Techniques for preventing homograft rejection may be directed at the recipient of the graft, at the donor animal, or donor tissue. Methods of treating the recipient usually are designed to depress or inactivate the reticuloendothelial, lymphoid, and bone marrow systems, and thus inhibit both phases of homograft rejection. These methods consist of: (1) saturation of the reticuloendothelial systems with particulate substances such as trypan blue, (2) removal of various organs such as the spleen, (3) diets deficient in amino acids, proteins, or pyridoxine, (4) radiations, (5) endocrine substances particularly cortisone, (6) chemicals and drugs including benzol, nitrogen mustard, and other cytotoxic agents, (7) treatment of the recipient prior to, or just after, birth to produce immunologic tolerance, and (8) creation of "the enhancement effect" by injection of tissues or tissue extracts prior to homgrafting.

Many methods have been used to render donor tissue incapable of calling forth a reaction on the part of the graft recipient. These include hypothermia, freezing, thawing, heating, dehydration, lyophilization, irradiation, treatment of the donor animal with drugs, and preservation of donor tissue in vitro prior to grafting. However, most investigators have been concerned with methods of conditioning the recipient to accept the donor tissue, and less attention has been paid to inducing the donor tissue to accept the new host.

Interest has also centered on the testing of drugs with and without supplementary roentgenotherapy for their effect on promoting growth of homologous tumor transplants in resistant animals. In a strain of rats with an induced immunity to the Bagg lymphosarcoma, conditioning with roentgenotherapy followed by cortisone reduced the animals' resistance to the tumor. No effect on this immunity has been noted when the animals were given sublethal doses of nitrogen mustard, triethylenethiophosphoramide, 5-fluorouracil, streptovitacin-A, cytoxan (cyclophosphamide), or combinations of nitrogen mustard and cortisone. Similar results were obtained in another strain of rats resistant to the same tumor.

This tumor, implanted into rats of these two strains, provides a system for screening drugs for their effect on immunity. Thus far experiments have not revealed a drug equal to or better than the combination of roentgenotherapy and cortisone as a conditioner for the recipient of a tumor homograft.

Perhaps, conditioning the donor and the recipient with agents developed in some such screening system will provide the key to successful homotransplantation of normal tissue. The destruction of host defense mechanisms sufficient to permit the permanent survival of homografts in an adult human being, and at the same time permit survival of the individual receiving the graft, may not be possible. At the present time this has not been proved or disproved and remains a challenge for surgical research.

OF CANCER AND VIRUSES

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CANCER, as a disease entity, presents the most complex and difficult challenge which the surgeon is called upon to face. The mode, the vigor, design, and direction of attack upon this entity, either in the general or specific sense, are conditioned by our concept of the nature of this bizarre disease. The surgical and radiotherapeutic approach to cancer is predicated upon the assumption, supported by morphologic observation, that cancer is a disease of cells, that some cells in a local site undergo transformation into cancer cells, and that if extirpation of this local cell group is carried out the patient will survive. This concept implies a local transformation, presumably due to local influences, in which a cell goes awry, producing daughters that no longer obey or conform to the laws of the body, thus demonstrating autonomy. These cells produce local phenomena by cellular proliferation and distant phenomena by cellular migration and implantation. The properties of proliferation and migration are properties of cells that respond to the stimulus of inflammation, such as the histiocytes, leucocytes, macrophages, and plasma cells. During recent years, some interest has been shown in the idea that neoplasia, in general, represents a type of ceullular response to some inciting agent in a manner somewhat resembling the cellular response to any inflammatory stimulus.

The recent demonstrations of the relationship between smoking and lung cancer have subtly implied that an agent in the smoke alters the bronchial epithelium in such a way as to promote the proliferation and migration of epithelial cells. This has been the latest in a long series of observations relating the origin of human and animal cancers to a presumably specific agent. It is probably not too far afield to state that most workers believe there are one or more agents which, when introduced into a receptive cell, will cause that cell to undergo changes characteristic of cancer. Tumors in chimney sweeps, aniline dye workers, Schneeberg cobalt miners and American smokers have been cited as examples of chemical carcinogen activity. However, none of these clinical examples, and few of the chemical carcinogen experimental cancers, have shed light upon the genetic, biochemical, or enzymatic alterations which have led directly to cancerous activity. Currently, the most acceptable thesis states that normal cells undergo transformation to autonomous malignant cells, but in laboratory animals, most autonomous tumors develop from pre-existing dependent tumors or precancerous lesions, and it is not beyond the realm of possibility that the same may eventually be noted to be true for human cancers. Should this become a fact, our thinking may have to be reoriented toward the possibility that chemical carcinogens may merely alter the recipient cell and thus make it susceptible to an agent which is able to cause genetic and somatic mutations which are transmissible to the daughter cells. It goes without saying that whatever imprint is made upon the original cell during its transformation must be transmitted through many generations. This transmission may be affected by an original genetic mutation that breeds true, or by nuclear-somatic transmission of the agent, or the agent's offspring, to the cellular offspring. The latter possibility, of course, suggests infestation with an agent such as a virus.

There has been fairly conclusive evidence that in experimental animals, a few cancers have viruses as their etiologic agent—mouse

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leukemia, rabbit papillomatosis, chicken sarcoma, mouse mammary tumor, frog renal carcinoma, and the multiple organ tumors caused by the mouse polyoma virus, to mention a few. These tumors have yielded the information that cancer viruses are not always similar to each other. The Rous sarcoma virus contains nucleic acid of the ribose type (RNA) while the Shope papilloma virus contains nucleic acid of the deoxyribose type (DNA). By using fluorescent antibodies, it has been possible to demonstrate that the mature virus is present only in the keratinizing (old) papillomatous cells in the rabbit papilloma, implying that in the young daughter cells the virus is present in an immature form.

It seems reasonable to expect that some human cancers will soon be proved to be due to viral infestation. Dmochowski has identified virus particles in human leukemia; Fortner has produced bile duct cancer in hamsters with human bile; Grace has produced malignant tumors in mice by cell-free extracts from human tumors; Powers has induced hyperplasia in hamsters by cell-free extracts from the sputa of patients with pulmonary cancer, and Mueller, Menefee, and Ivler have observed virus-like particles in human colon cancer.

The method of establishing that any viruses recovered from human cancer have etiologic relationship to that cancer is bound to be extremely tedious. At present there is no good description of the morphologic response of a cell to the presence of tumor viruses. Grossly, it is possible to note that cell proliferation and migration occur, and this effect can be noted in the whole animal. Microscopically, there has been no consistent intracellular response to the presence of these viruses and such response, if any occurs, should be observable. Ordinarily we conceive of the use of Koch's postulates when thinking of the identification of bacteria as etiologic agents for disease, and such orientation has been brought into the infectious virus field. Such opportunities to test the carcinogenic activity of suspected human tumor viruses will be difficult to get, and methods other than human experimentation will have to be devised in order to obtain the required information.

Should the viral etiology of some human cancers be established, its importance to the surgeon is difficult to assess. Such an etiology may well suggest that cancer is a systemic disease, whose local manifestations occur because local trauma at the cellular level has set the stage. A precancerous state may thus be a prerequisite to the development of cancer, and if this proves to be true, our attention may well be directed toward extirpation of all such precancerous states, rather than toward antiviral therapy of established disease.

THE SURGEON AT WORK

BUNION, HALLUX VALGUS, AND METATARSUS PRIMUS VARUS

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IT IS FOLLY to force a normal foot year after year into a modern narrow, pointed, or short and high heeled shoe and expect that foot to remain normal in appearance and function.

Although all authorities agree that footwear plays a very important role in causing hallux valgus and bunion formation, there is always a constitutional tendency to most of the conditions affecting the feet, and, in hallux valgus, metatarsus primus varus is considered to be a predisposing and hastening factor.

However, the fact remains that bunion and hallux valgus often develop without metatarsus primus varus as seen in 22 of 26 feet operated on.

PATHOLOGIC ANATOMY

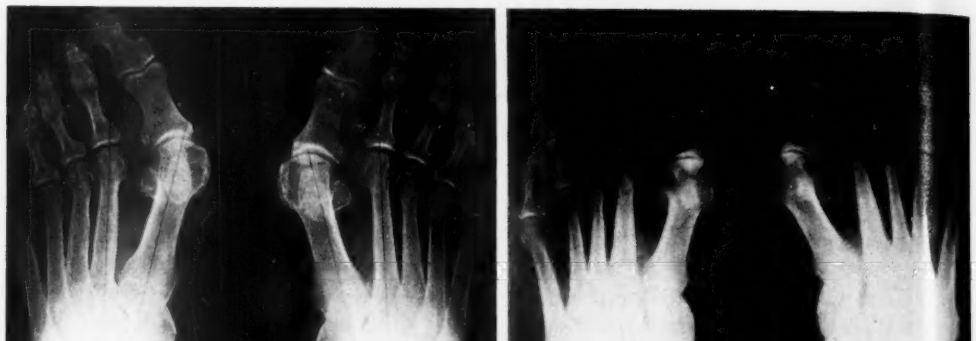
No matter what the initiating cause, whether hereditary predisposition, metatarsus primus varus, muscle imbalance, faulty footwear, or even hose, it is imperative that the mechanism responsible for maintaining the hallux valgus be analyzed and comprehended if a proper line of treatment is to be pursued. The pathologic changes that develop in hallux valgus are mainly responsible for maintaining the deformity.

Bone changes. There is enlargement of bone over the medial aspect of the first metatarsal as well as an increase in the intermetatarsal angle. The excess bone formation is accompanied by cystic degeneration of bone as in osteoarthritis. Actually, osteoarthritis is a late complication of hallux valgus with erosion of the cartilage lipping and osteophyte formation. The lateral sesamoid bone is displaced laterally and becomes hypertrophied (Fig. 1).

Joint changes. Due to the adduction of the big toe the metatarsophalangeal joint subluxates laterally in advanced cases (Fig. 1a). The osteoarthritic lipping and osteophyte formation mentioned under bone changes are obvious at the base of the proximal phalanx. The medial part of the joint capsule is stretched and lengthened while the lateral part with the collateral ligament is contracted and at times buckled and adherent. The interphalangeal joint of the big toe may be adducted, too, and the metatarsophalangeal joint extended. The big toe is also rotated inward on its long axis, sometimes as much as 80 degrees; the toenail may face medially. The adjacent second toe may develop dorsal subluxation if it overrides the big valgus toe. One or more hammer toes are a frequent accompaniment.

Soft tissue changes. Callosities and corns are found over the ball of the foot and dorsum of the toes or between them due to pressure of one toe against the other. When the skin is subjected to unusual pressure, such as the compression of the skin over the olecranon between the bone and a hard object, or the skin over the medial aspect of the head of the metatarsal between the bone and the narrow shoe, a corn or an adventitious bursa or both may develop.

This is nature's reaction: the bunion of the big toe is a protective mechanism whereby the bursa will act as a buffer and shock absorber to prevent injury to the vulnerable tissues, namely, skin. Further pressure and irritation lead to bursal inflammation which may progress to suppuration, rupture, and sinus formation.



a b

FIG. 1. a, Note the cystic changes in the head of the first metatarsus and the excess bone on its medial aspect. b, The lateral sesamoid is displaced laterally and osteoarthritic changes of the joint are obvious as is the subluxation.

The most significant changes that take place in the soft tissues are those involving the tendons. These changes plus those in the lateral capsular ligament, together with continued faulty footwear are, most probably, the main factors responsible for the progressive hallux valgus deformity after it has developed. On these observations is based the line of treatment to be described fully.

The high heeled pointed shoe (Fig. 2) splints the ankle joint into 55 degree plantar flexion and the metatarsophalangeal joints of all the toes into a nearly equal angle of dorsiflexion or extension as well as a varying degree of adduction of the big toe, depending on the shortness, narrowness, and pointedness of the shoe. The degree of ankle flexion and extension of the toes also varies with the height of the heel. This position is responsible for the following six pertinent changes:

1. Contracture of the lateral capsular ligament occurs.

2. There is lengthening of the medial capsular ligament.

3. Moderate contracture of the extensor hallucis longus tendon is noted because the amount of flexion in the ankle will neutralize the extension in the metatarsophalangeal joint of the big toe; and since this long tendon crosses both joints, namely the ankle and the metatarsophalangeal joint of the big toe, the moderate contracture produced is due mainly to the adduction of the big toe. This tendon is displaced laterally, and the correction of the valgus will throw it into tension. In the deformed position it starts acting as an adductor as well as an extensor (Fig. 3).

4. If the extensor hallucis brevis is examined it is found to arise distal to the ankle joint and cross the constantly extended and adducted metatarsophalangeal joint. Since it arises from the lateral aspect of the foot, it runs an oblique course and acts as an adductor; the contracture in it becomes pronounced as the hallux valgus and lateral subluxation progresses and is an important factor in maintaining the deformity. This is a very constant and obvious finding during the operative procedure. A vicious circle develops as both the contracture and the valgus deformity aggravate each other.

5. The adductor hallucis is a strong muscle with a strong short tendon inserted into the ventrolateral aspect of the base of the proximal phalanx; this muscle by the nature of its position and action contracts in the valgus deformity and

is subject to the same vicious circle mentioned above.

6. The abductor hallucis and flexor hallucis brevis and longus are also displaced laterally but do not play a significant role in maintaining the deformity.

SYMPTOMS

The symptoms of bunion, hallux valgus, and metatarsus primus varus are not due to any one of these conditions per se nor are they due to the combination of them all. A foot with these deformities is painless if shoes are not worn, or even if accommodating shoes are worn.

The pain is due to one of the following conditions:

1. The adventitious bursa (bunion) becomes inflamed, swollen, and painful from continued irritation. The overlying skin becomes hyperemic and shiny. A corn may develop over it and aggravate the condition. Bursitis may become purulent and require drainage. If the bursa is inflamed, the pain is not relieved by taking the shoes off.

2. Corns and callosities on the dorsum of the other toes or between the first and second toes or on the ball of the foot are responsible for pain on weight bearing and on the wearing of shoes.

3. A hammer toe may be painful and need correction.

4. Osteoarthritis of the metacarpophalangeal joint of the big toe causes stiffness and burning pain.

5. The difficulty in obtaining properly fitting shoes plus pain from any one of the conditions mentioned will lead to disturbance of proper weight bearing which in turn may cause continuous pain in all the forefoot—anterior metatarsalgia. The pain may radiate to the dorsum of the foot.

6. The patient tries to walk on the lateral aspect of the foot. This will throw the strain on the ankle, causing pain in the ankle and perhaps in the hip and also in the lower part of the back.

7. On account of inward rotation of the big toe, ingrowing of the medial aspect of the toenail develops; this causes pain and may lead to infection and granuloma formation.

The only substantial measure to prevent deformities is proper footwear, especially in childhood and early adult life.

FIG. 2. Roentgenogram of a lateral view of a foot in a high heeled shoe. Note the 55 degree extension in the toes and the equal amount of plantar flexion at the ankle.

NONOPERATIVE TREATMENT

If a bunion develops with or without a variable degree of hallux valgus, the patient usually does not seek medical advice until the pain from bursitis, corns, or ingrowing toenails develops. For any one of these complications, the footwear has to be changed; the patient must stay off the foot or feet for a few days and the complication is treated accordingly. Against recurrence, properly fitting shoes are the only guarantee. If there are any other abnormalities of the feet, e.g., improper posture, flat feet, small muscle imbalance, or corns, these should be attended to.

Bunion with bursitis and no hallux valgus is not too common. If it exists per se, it can be treated conservatively provided the patient is co-operative and reasonable. Unfortunately, most patients refuse to abandon the attractive modern shoes that splint their feet in the most uncomfortable and injurious position for hours on end; that is why most of the cases a surgeon handles are advanced and need operation to correct the condition.

OPERATIVE TREATMENT

Bunions. A bursa with a variable amount of exostosis and no valgus is infrequently encountered and operated on. Of 26 patients only 4 had simple bunions that needed operation. Since these patients have no hallux valgus or metatarsus primus varus, the corrective procedure is simple and is described in all the books and

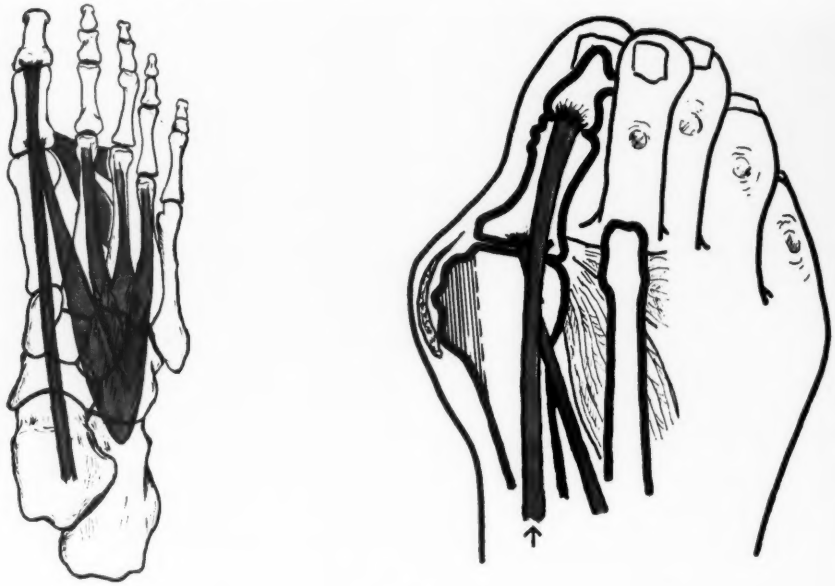


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FIG. 3.

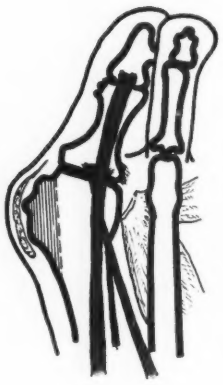


FIG. 4.

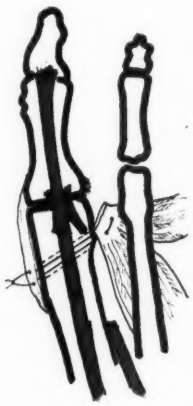


FIG. 5.

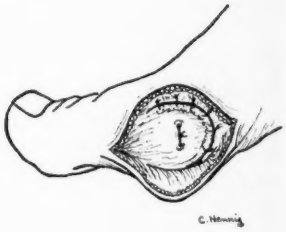


FIG. 6.

FIG. 3. a, Normal position of extensor hallucis longus and extensor hallucis brevis tendons. b, The arrow points to the displaced extensor hallucis longus which acts as a bow string and effects adduction.

FIG. 4. Diagram showing the anatomy of the big toe after interruption of the conjoined adductor flexor tendon. The shaded area in the head of the first metatarsal represents the exuberant bone that has to be chiselled away.

FIG. 5. The diagram shows the Z lengthening of the extensor hallucis longus, the complete interruption of the extensor hallucis brevis, the excision of the bunion, and correction of the subluxation and valgus. The wire suture is seen before tightening to anchor the adductor tendon to the lateral aspect of the metatarsal head and to fix the capsuloperiosteal flap medially under tension and maintain the overcorrection.

FIG. 6. Diagram illustrating the last stage in the repair of the capsuloperiosteal flap. It may be noted that the wire suture which anchored the adductor tendon to the metatarsal head laterally is now tied in the center of the flap medially.

articles that deal with this subject. Through a dorsomedial incision over the bunion a U-shaped capsuloperiosteal flap with the bursa is elevated from the enlarged medial surface of the head of the metatarsal with a sharp scalpel, not a periosteal elevator, leaving its base attached to the base of the proximal phalanx. The underlying exuberant osteochondromatous mass is chiselled level (Fig. 4, 5, and 6) and the bursa, if very large, is excised. Otherwise the bursa is left alone. The flap is sutured back under tension to the periosteum of the first metatarsal. The toe is immobilized with a medial tongue blade in moderate abduction for 7 days. The patient is allowed out of bed, and weight bearing is started progressively on the third day postoperatively. Figure 7 shows roentgenograms made before and after such an operation.

Bunions with hallux valgus. Eighteen such feet were treated and the pathologic anatomy was observed. Some patients were followed up regularly, and both surgeon and patient were satisfied with the results. The patients have no pain, the cosmetic result is very satisfactory, and the function is definitely improved in all. Those who were unable to dance can dance again. The postoperative period of partial disability was short. The principle behind this procedure is the noninterference with the main components of the metatarsophalangeal joint, namely, the head of the metatarsus and base of the proximal phalanx.

First, under tourniquet ischemia, an incision about 1½ inches long is made on the dorsum of the first web and carried down to the space between the metatarsophalangeal joints. The digital nerves lie on either side of the incision and only small vessels have to be interrupted and ligated. In the depth of the wound a wide space is found occupied by an empty, very thin walled bursa overlying the conjoined tendon of the adductor hallucis and flexor brevis. The size of the space and bursa is proportional to the degree of metatarsus primus varus. The tendon is exposed and detached from its insertion into the base of the proximal phalanx with a sharp No. 15 blade. This tendon is very broad and all the fibers should be interrupted. To assure interruption the assistant must abduct the big toe and put the tendon on tension. Careful inspection always reveals more fibers left on the plantar aspect of the phalanx. To secure full correction and overcorrection, no fibers should be left unsevered.

a b

FIG. 7. A case of bunion and no hallux valgus or metatarsus primus varus. a, Before, and, b, after bunionectomy.

The tendon bulk is dissected from the joint capsule further proximally to assure its retraction, if well freed it retracts to the head of the metatarsal. This tendon will be dealt with at a later stage.

The second step is taken while the assistant is still abducting the big toe. The surgeon divides the lateral capsular ligament; the complete severing of this ligament allows further abduction of the valgus toe.

The third step involves the extensor tendons of the big toe which are exposed by medial retraction of the medial skin flap of the same wound. Care should be given to avoid the digital nerve which lies just lateral to the tendons. The extensor brevis at this level is broad and lies in a separate synovial sheath medial to the longus but slightly overlapped by the latter. The extensor brevis is completely interrupted and left unrepaired. This tendon is under great tension, it retracts far proximally after its division, and its interruption greatly facilitates the correction of the valgus. Attention is then directed to the extensor hallucis longus, which is easily exposed; its synovial sheath is slit longitudinally, and a Z-shaped incision about 1 inch long is made for the purpose of lengthening this tendon. Usually a ½ inch lengthening is needed. The amount of the lengthening needed varies with the degree of extension and valgus. Repair of this tendon is left to a later stage.

a b

c

FIG. 8. Photographs of a foot, a, before and, b, 2 years after bunionectomy and correction of the hallux valgus. c, Roentgenograms of feet before and after operation.

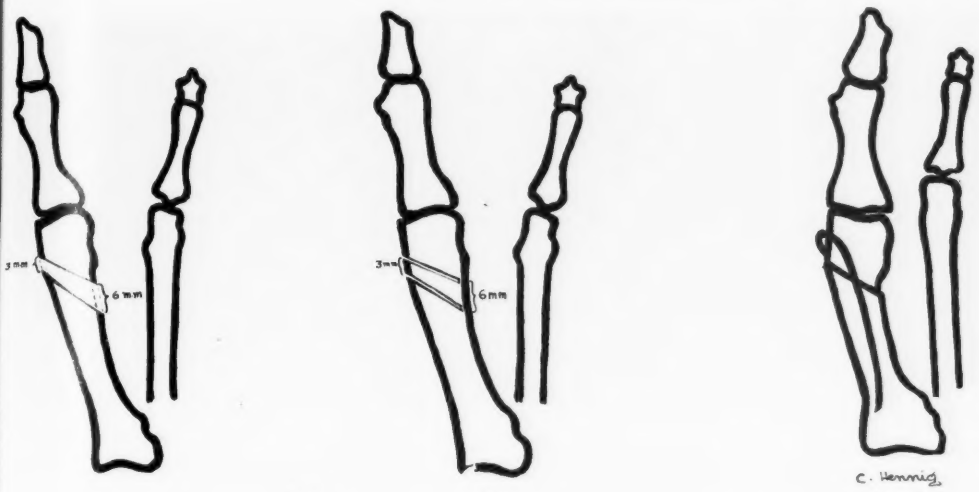
In the fourth step, another 1½ inch curvilinear incision is made over the medioplantar aspect of the metatarsophalangeal joint, instead of mediodorsally, in order to leave a wider strip of skin between the two incisions, thus assuring better vascularity. The bunion is exposed and dealt with in the usual manner: a U-shaped flap with or without the bursa is elevated and the exuberant bone is excised.

The head of the metatarsal shows a demarcation line between the articular surface and the nonarticular medial part; this latter part only should be excised. When excising this bone, a sharp osteotome is used, starting proximally and aiming at the demarcation line. Precision is important here. The optimum amount of bone should be removed and one should avoid letting the osteotome wander into the head of the metatarsal. If the cartilage over the rest of the bone is degenerated and flaking it should be shaved off with the scalpel. Tension on the periosteocapsular flap will easily correct the valgus and any subluxation of the joint. The capsular flap is anchored under tension as will be described.

In the fifth step the capsular flap medially and the adductor tendon laterally are dealt with. One way of anchoring both of these structures in their proper places is as follows: A fine drill hole is made in the head of the metatarsal 1 centimeter proximal to the articular surface, a mattress suture of No. 30 stainless steel or preferably braided tantalum wire is applied to the adductor tendon; the two ends of the wire are brought out medially and threaded on an empty straight needle which has been passed retrograde from the medial opening of the drill hole in the metatarsal head. When the needle is pulled out, the two ends of the wire are pulled out with it, and the adductor tendon is anchored to the head of the first metatarsal. The free wire ends are each threaded to a separate needle and passed through the capsular flap 3 to 4 millimeters apart while optimum tension is applied to the flap and the big toe is abducted to achieve slight overcorrection. The wire is then tied securely over the flap. The edges of the flap are sutured to the surrounding periosteum and capsule with interrupted No. 3-0 or 4-0 silk sutures. At this stage the abductor hallucis tendon may be shortened.

The transfer of the adductor tendon serves two purposes. First, it may avoid recurrence of valgus by eliminating adduction of the big toe and second, it may prevent or correct a small degree of metatarsus primus varus.

The sixth step consists of repair of the elongated extensor tendon with either buried wire or fine silk interrupted sutures. An optimal degree of lengthening is necessary. Too much lengthening will deprive the big toe of the only extensor power remaining. The synovial sheath is approximated over the tendon with a few fine interrupted silk sutures. The skin is repaired. A pressure dressing is applied, and the tourniquet is removed. The toe is immobilized in abduction as described previously.



a FIG. 9. b FIG. 10.

FIG. 9. a, Note the position of the big toe after correction of the hallux valgus in a case of metatarsus primus varus before removal of the wedge indicated in the diagram. This position is incompatible with a normal shoe which is going to force the big toe back into valgus; moreover, it is unsightly. b, This diagram shows the best way of performing an oblique wedge osteotomy. Note how the two cuts in the bone are made short of the lateral cortex before carrying one all the way through.

FIG. 10. The final stage of the osteotomy after fixation with an intramedullary Rush nail. Note the reduction in the intermetatarsal angle and the length of the first metatarsal.

Exercise of all the toes is encouraged on the second day. Progressive weight bearing is commenced on the third or fourth day. The sutures are removed on the eighth day, and the immobilization is discontinued on the fourteenth day.

Figure 8 shows photographs and roentgenograms of feet before and after such an operation. Both feet may be corrected at one operative session.

Metatarsus primus varus with bunion and hallux valgus. Surgical treatment of metatarsus primus varus is essentially a wedge osteotomy and is indicated only if the condition is associated with symptomatic hallux valgus and bunion formation and when the intermetatarsal angle is greater than 15 degrees. For an angle between 10 and 15 degrees osteotomy is not necessary.

The procedure includes that for bunion and hallux valgus described previously plus a little variation and two additional steps. The variation concerns the adductor tendon and the additions are (1) oblique wedge osteotomy of the first metatarsal bone and (2) excision of the lateral sesamoid bone.

Distal osteotomy of the first metatarsal bone as a treatment for metatarsus primus varus is by no means a new procedure. A distal osteotomy similar in principle was described by Hohmann in 1924 and by Peabody in 1931. Hawkins described it again in 1945. Lapidus in 1934 described a lateral wedge osteotomy from the first metatarsocuneiform joint to correct the abduction or primus varus.

The operative procedure is carried out as for bunion and hallux valgus. When the conjoined flexor adductor tendon is completely severed, the displaced lateral sesamoid bone in this tendon is excised with a sharp No. 15 blade; to facilitate this step, the free end of the tendon is pulled dorsally, thus elevating the sesamoid bone from the plantar aspect of the foot. The excision of this bone is not an easy procedure and one must be very careful not to injure the plantar structures by keeping the scalpel at the surface of the bone while dissecting the latter. The bone may be grasped with a small Kocker clamp and pulled dorsally in the wound. The excision of this bone will help the displacement wedge osteotomy that is to be described.

The extensor tendons are dealt with as pre-

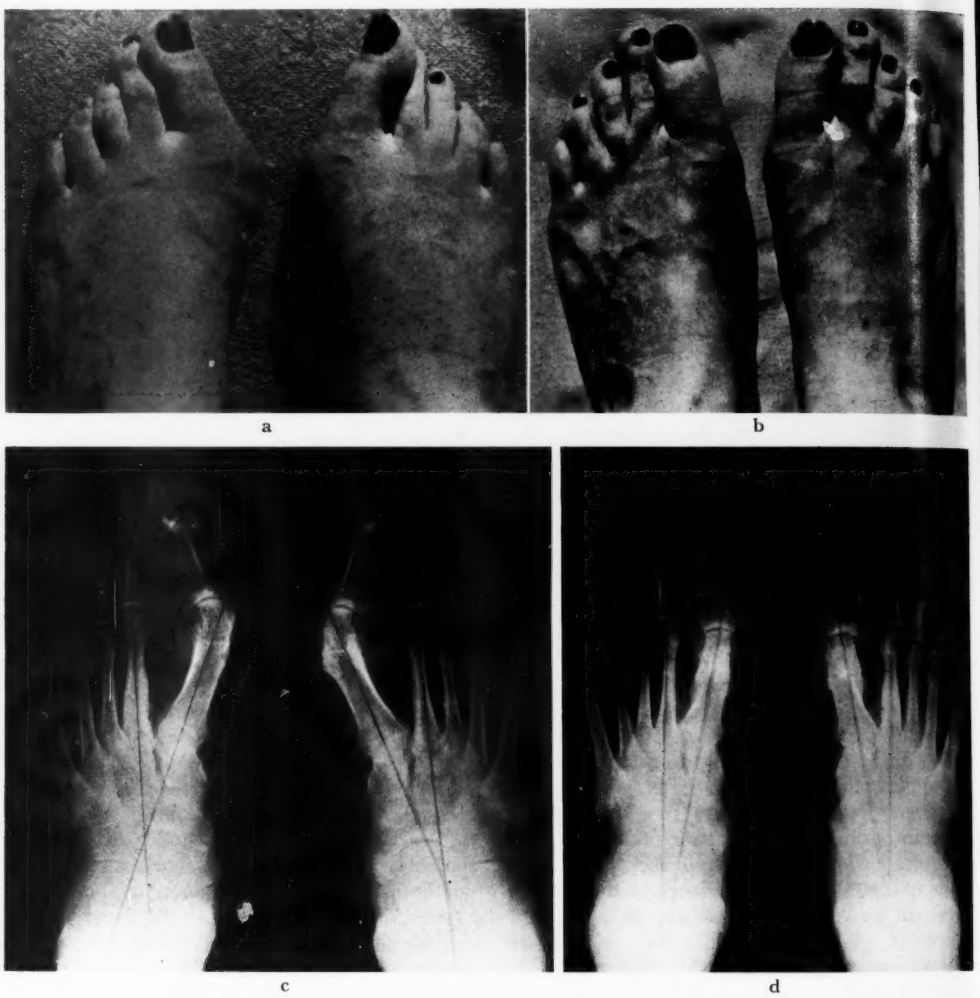
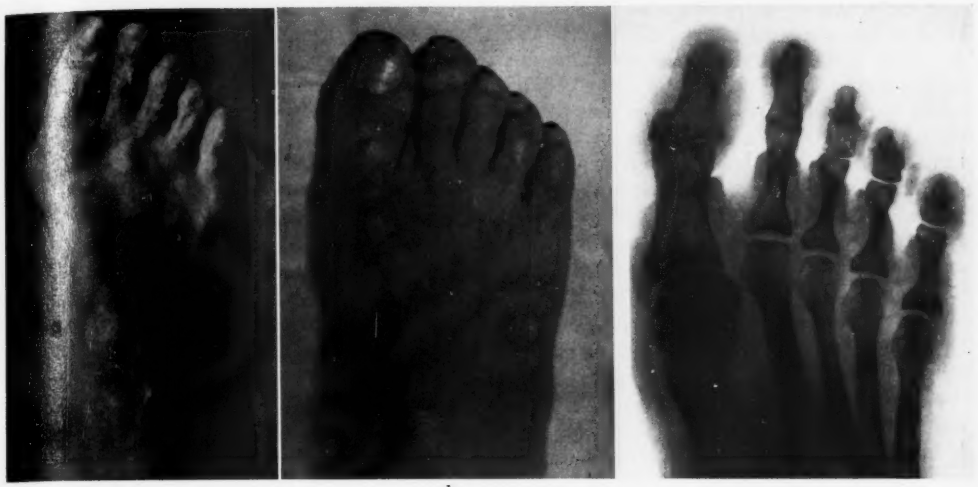


FIG. 11. Photographs and roentgenograms of both feet before and after correction of bunions, hallux valgus, and metatarsus primus varus. Postoperative pictures were taken 18 months after operation. A previous bunionectomy performed elsewhere without correction of the deformity did not relieve the symptoms. Note the reduction in the intermetatarsal angle and the length of the first metatarsal as well as the correction of the rotation in the big toe and excision of the lateral sesamoid bone. The metatarsal angle is reduced from 22 to 10 degrees by wedge osteotomy. The Rush nails were removed 4 months after operation.

viously outlined. The bunion is also excised, and the periosteum is elevated around the neck of the first metatarsal just below the site of the resected exostosis. An oblique wedge osteotomy is planned for excision of a segment from the metatarsal bone in such a manner as to achieve adduction of the distal segment of the metatarsus thus correcting the varus position. This oblique wedge displacement osteotomy is a necessary step in correcting the hallux valgus associated with a varus first metatarsal because, after aligning the big toe with a pronounced varus metatarsal (15 to 25 degrees at the first intermetatarsal angle) by the procedures described for



a b c

FIG. 12. Photographs and roentgenogram of a foot before and after bunionectomy and wedge osteotomy. The Rush nail was removed 5 months after operation.

hallux valgus, the toe points far out medially (Fig. 9), a position incompatible with an ordinary shoe. The wedge osteotomy is to correct this position as well as to prevent recurrence, because the big toe would deviate again and cause further trouble when shoes are worn, if the osteotomy were omitted.

The osteotomy technique recommended produces adduction of the distal metatarsal segment with some shortening of the bone and correction of the rotation. The shortening of the bone reduces the amount of lengthening needed in the extensor hallucis longus. The wedge should measure 2 to 3 millimeters medially and 5 to 6 millimeters laterally. These measurements may be slightly varied depending on the degree of metatarsus varus and length of the metatarsus. Too much shortening is to be avoided because it would put the metatarsophalangeal joint at a more proximal level which might interfere with the mechanics of walking.

The wedge osteotomy is made obliquely with the electric saw, and the osteotomy is performed short of the lateral cortex, before removing the wedge completely because, after one osteotomy has been made all the way through the bone, the second osteotomy for removal of the wedge is very difficult to make because of the instability of the bone following a complete first osteotomy.

No drill hole is made in the head of the metatarsal for anchoring the adductor tendon. The head of the metatarsal is displaced and fixed with an intramedullary Rush nail (Fig. 10), a Kirschner wire, or a stainless steel wire suture passed through drill holes on either side of the osteotomy as described by Mitchell and associates. The oblique wedge osteotomy is more difficult to make than the straight wedge osteotomy but it unites sooner and prevents the medial displacement of the distal segment if it is not securely fixed. The lateral sesamoid bone, if not removed, will interfere with the lateral displacement of the distal segment. After the bone is fixed with a Rush nail, the adductor tendon is sutured to the periosteum over the lateral aspect of the metatarsal head with two fine wire or silk sutures and the capsuloperiosteal flap is repaired as previously described.

Figures 11 and 12 show photographs and roentgenograms of feet before and after correction of the bunion, hallux valgus, and metatarsus primus varus. This operation is preferably done one foot at a time with a 3 to 4 month interval.

The first metatarsal wedge osteotomy produces an appreciable reduction in the width of the forefoot and makes it possible to fit the foot into narrower, more attractive shoes. The pressure dressings are applied before removing the tourniquet, and the big toe is immobilized in the slightly overcorrected position with a tongue

blade for 8 days without weight bearing. Exercise of all the other toes is encouraged early. On the eighth day the sutures are removed, and a walking plaster cast is applied for 4 weeks. The patient can start light duties after the cast is applied provided that not much walking or standing is required. Only office workers can return to work early, and these patients are instructed to elevate the foot on another chair while sitting. In the cast the big toe should be exercised. The cast is discarded at the end of 5 weeks postoperatively and daily physiotherapy is started. Shoes one size larger have to be worn for about 2 months because of mild residual swelling. The Rush nail may be removed under local anesthesia 4 to 6 months later.

Patients in the painful advanced conditions are overjoyed with the results of this operation, from the standpoint of both the clinical and the cosmetic outcome.

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THE PREVENTION OF POSTRESECTION SPACES FOLLOWING RESECTION FOR PULMONARY TUBERCULOSIS

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ALTHOUGH no precise definition has been agreed upon, it is generally stated that when full expansion of the lung has not been achieved within 2 to 3 weeks of pulmonary resection a persistent pleural space exists. This complication varies from as high as 60 per cent incidence after wedge resection to 22 per cent after lobectomy and segmental resection. The seriousness of the condition depends upon whether or not a bronchopleural fistula exists. If it does not, it is generally agreed that such a persistent pleural space is asymptomatic and benign.

Since persistent pleural space has not been found to be a serious problem in the present series and since a brief review of the literature on this subject revealed striking differences in the approach to this complication, it was believed that a review of the prevention and management of the persistent pleural space might be of value.

CLINICAL MATERIAL

One hundred and sixty-four consecutive resections for pulmonary tuberculosis were reviewed. The ages of the patients varied from 10 to 63 years, the majority of resections being performed in the 20 to 40 year age group. Almost half of the patients were North American Indians. One hundred and fifty patients had positive sputum upon admission to the sanatorium and 50 were still positive and also drug resistant at the time of operation.

In this consecutive series of resections an overall incidence of persistent pleural space of 7.3 per cent was recorded (Table I). The highest incidence followed segmental resection or segmental resection combined with lobectomy. For that reason these two procedures are not tabulated separately. The next highest incidence followed right upper lobectomy which really combines lobectomy with segmental resection, because of the inevitable raw surface left between the upper and middle lobes. The importance of this raw surface is emphasized by the fact that a pleural space never persisted after left upper or either lower lobectomy. Since wedge resection is an unanatomic and potentially dangerous procedure in pulmonary tuberculosis, particularly when such an anatomically and pathologically acceptable procedure as segmental resection is available, I do not use it. In order to remove a tuberculous lesion by wedge resection it is almost impossible not to transgress diseased tissues, unless the lesion is so small that surgery is debatably necessary to begin with.

Of the 12 persistent pleural spaces 2 were overt bronchopleural fistulas and needed further surgical treatment. One of the patients was cured by postresection thoracoplasty for a bronchopleural fistula which developed after a left apicoposterior segmental resection. The second patient died after an unsuccessful Schede thoracoplasty for a bronchopleural fistula which developed after a right upper lobectomy, apical lower segmental resection, and concomitant thoracoplasty. Thus the "symptomatic" persistent pleural spaces in this series of resections were 2 in 164 resections or 1.2 per cent.

Of the 12 persistent pleural spaces 10 were bronchiolar or alveolar leaks, and none of these needed any special procedure for their management, even though several were still present after 1 year. All of these spaces were benign, in that the patients' sputa remained negative, even though when most of the patients were discharged from the sanatorium the spaces were still present. These patients remained well at the time of review. Thus, "asymptomatic" persistent pleural spaces in this series of consecutive resections were 10 in 164 resections, or 6.0 per cent.

The incidence of persistent pleural space was

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TABLE I.—INCIDENCE

Resection procedure	*No.*	*Thoraco-plasty*	*Phrenic nerve crush or resection*	*Persistent pleural spaces*
Right upper lobe	51	10	4	3
Left upper lobe	15	10	3	0
Other lobes (lower and middle)	10	—	2	0
Segmental, including lobectomy and segmental resection	88	12	6	9
Totals	164	32	15	12

not influenced by age, sex, race, or bacterial content of the sputum but rather by the operative procedure, namely segmental resection or similar operation, i.e., right upper lobectomy. In these operations large raw surfaces of lung tissue remain after removal of the diseased lung, and alveolar and bronchiolar air leaks are frequent.

PREVENTION AND MANAGEMENT OF THE PERSISTENT PLEURAL SPACE

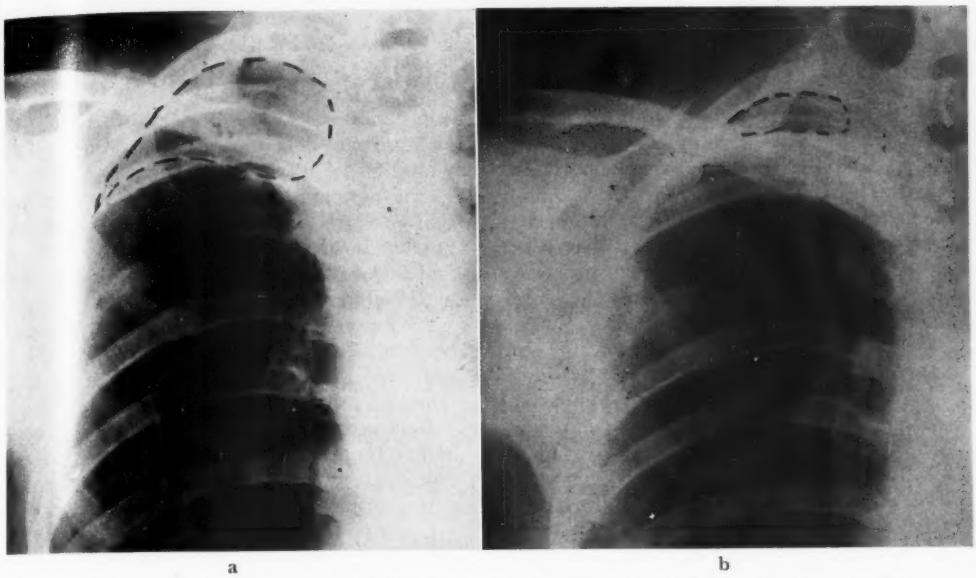
Preoperative preparation. Preoperative bronchoscopy is routine in all patients who are to have pulmonary resection, in order that active endobronchitis can be excluded. The high incidence of tuberculous disease recognizable at the suture line, even when active disease is not seen bronchoscopically, makes this step an absolute prerequisite. It is surprising, however, how often bronchoscopy is neglected. Since many patients, almost 30 per cent in this series, come to surgery with positive and drug resistant sputum, the importance of this step cannot be overemphasized.

Preoperative bronchography is performed in about 80 per cent of patients, particularly if tomography leaves some question as to the extent of the disease. The purpose of bronchography is to delineate the diseased segment or lobe and also to determine the state of the adjoining bronchial tree. Bronchography will do this much better than inspection of the lung tissue at operation. If an adjoining segment is fibrosed, bronchiectatic, or emphysematous, it is much better to remove that segment along with the one in which the major disease process is localized; otherwise, postoperative expansion problems are being invited.

Preoperative physiotherapy is valuable and can be taught by the nursing staff if physiotherapists are not available. Emphasis is placed upon diaphragm control, deep breathing exercises, and coughing techniques. If these are well taught before operation and strictly applied in the postoperative period rapid re-expansion of the remaining lung is considerably enhanced.

Operative considerations. The resection of any part of the lung, no matter how small, creates a space which must be filled by expansion of the adjacent parenchyma, mediastinal shift, and a rise of the ipsilateral portion of the diaphragm. Therefore, as little lung tissue as possible should be excised and the anatomically and pathologically preferable operation is segmental resection. If adjoining segments are diseased, one or more must be removed or a lobectomy performed in preference. The raw surfaces of lung tissue must be carefully inspected for bronchiolar leaks and all such areas carefully transfixed and oversewn with fine atraumatic silk. The bronchus must be cut off flush with its parent trunk, carefully closed with silk or wire, and covered with adjacent tissue and a pleural flap. Once all these measures have been carefully attended to, a decision must be made, while the patient is on the table, as to how much disproportion is going to remain between the size of the chest cavity and the capacity of the remaining lung to fill that space. If the patient is elderly or the surrounding lung is fibrotic or emphysematous, the compensatory mechanisms will often be inadequate. In such cases the chest cavity must be tailored to fit the potential of the remaining lung tissue. The following measures have been proved to be of value.

1. Chest drainage. This must be adequate and prolonged or, if the space develops after removal of the original tube, reinstituted by means of a large trocar and cannula. I routinely use only one apicobasal tube, a No. 40 French whistle-tip rubber catheter, and attach it to suction with 25 to 30 millimeters of mercury, which is maintained until the space is obliterated and all air bubbling ceases. Should bubbling continue after 5 to 7 days, suction is discontinued but the tube is left in situ for a further few days and the space is watched by daily chest roentgenogram. Unless an overt bronchopleural fistula is present, the space will not increase but will either remain stable or show regression. These small pleural spaces represent minor bronchiolar fistulas which tend to persist for months after operation, are so far distal in the bronchial tree that infection is very rare, and can be safely treated expect-



a b

FIG. 1. a, Apical space 4 months after right upper lobectomy. Patient refused thoracoplasty. b, Same space 4 months later. Patient is asymptomatic, the sputum is negative, and he is back at work.

antly, in my experience, without any exception (Fig. 1).

2. Posture. Unless a major discrepancy between lung tissue and chest cavity exists after removal of one or two segments or a contracted upper or lower lobe, nothing more is done than to nurse the patient head down, 15 to 30 degrees from the horizontal, for at least 48 hours. This position is well tolerated by the patient, since he awakes from sleep in Trendelenberg position, but in the occasional nervous patient, posture is commenced preoperatively to familiarize him with it. This posture has been shown clearly to decrease the size of the dependent hemithorax and, I believe, is largely responsible for a low incidence of persistent pleural space.

3. Phrenic crush or resection. Dire consequences have been predicted by investigators who deplore phrenic interference. I have found no greater incidence of respiratory complication, i.e., paradox, atelectasis, or interference with raising sputum in those in whom the phrenic nerve has been cut or crushed than in those in whom it has not. Atelectasis developed in 4 patients in this series and none had had phrenic interference. Fifteen patients had their phrenic nerves either resected during lower lobe resections or crushed, as shown in Table I. This procedure is a valuable adjunct to diminishing the chest cavity-lung tissue discrepancy and also probably prevents compensatory emphysema, bronchiectasis, and occasional activation of latent disease in nearby lung tissue. The value of phrenic crush or resection is also supported by Belsey. The high incidence of uncomplicated inadvertent phrenic paralysis, particularly after right upper lobectomy, merely emphasizes that interference with the phrenic nerve, although not to be considered lightly, is not always deplorable if it is of therapeutic benefit.

4. Thoracoplasty. Of the 32 thoracoplasties performed in this series, 1 was carried out preoperatively to enable a patient with active endobronchitis to heal, so that resection could be performed later; 2 were performed postoperatively for overt bronchopleural fistulas; and the remaining 29 were carried out concomitantly with resection (Table I). A tailoring thoracoplasty of the osteoplastic type is the procedure of choice and adds only a few minutes to the operation. It leaves a stable chest wall so that atelectasis and paradox are rare and deformity is negligible. I place osteoplastic thoracoplasty next to routine posture as the most important single measure in

preventing the development of a persistent pleural space.

It should be stated here that a high incidence of persistent pleural space and bronchopleural fistula implies that resectional surgery is being performed when a thoracoplasty would have been a preferable operation for that particular patient. There is still a place for thoracoplasty in the treatment of pulmonary tuberculosis, and for osteoplastic thoracoplasty in particular. When a proper balance is maintained between resectional and collapse therapy, serious space problems almost cease to exist.

5. Other procedures. I have never found pneumoperitoneum to be necessary or desirable, so I cannot argue with those who do. Similarly, I have not had recourse to plombage, pleural tents, or diaphragmatic advancement. All of these measures aim to reduce the discrepancy between the pleural space and the lung tissue and, if they satisfy that function in the hands of their devotees, they should be continued, since no single method of management has been found universally applicable. Indeed, the prevention of this complication depends upon a number of variables which must be applied to each patient as an individual.

SUMMARY AND CONCLUSIONS

A persistent pleural space exists when full re-expansion of the lung has not been achieved within 2 to 3 weeks of resection.

"Asymptomatic" or benign persistent pleural space follows 6.0 per cent of resections, the greatest incidence after right upper lobectomy and segmental resection. These spaces never need further treatment.

"Symptomatic" persistent pleural space or bronchopleural fistula follows 1.3 per cent of resections. These spaces always require additional surgery.

Careful preoperative preparation of the patient and a proper balance between resection and thoracoplasty aid in reducing the incidence of persistent pleural spaces.

Concomitant phrenic crush or resection, osteoplastic thoracoplasty, and postoperative posture with strong positive pressure chest drainage are all complementary in the prevention and management of such spaces.

COMPOSITE RECONSTRUCTION OF THE FEMORAL ARTERY WITH SAPHENOUS VEIN AFTER ENDARTERECTOMY

W. STERLING EDWARDS, M.D., F.A.C.S., Birmingham, Alabama

THE RECONSTRUCTION of circulation in legs with segmental obliterative arteriosclerosis has been an important surgical advance of the past decade. The larger vessels in the abdomen, the terminal aorta, and iliac arteries lend themselves to very satisfactory long term results from graft replacement or bypass or to thromboendarterectomy. It is the obliterated femoral and popliteal artery that has presented the greatest challenge.

Saphenous vein autografts were tried early in the history of direct surgical treatment of femoral arteriosclerosis, first as replacement for the occluded femoral segment, then, at the suggestion of Kunlin, as a bypass shunt. Shaw and Wheelock were among the first to report a high incidence of late occlusion from replacement vein autografts which they attributed to the small size of the vein. Among the present most enthusiastic supporters of autogenous vein bypass grafts is Dale who reports 6 (19 per cent) early failures and 7 (22 per cent) late failures for a total of 41 per cent failures in 31 consecutive patients. This figure is discouraging.

Femoral artery homografts were enthusiastically adopted for several years, but again the early and late failure rate was discouraging. Szilagyi and associates clearly demonstrated that femoral homografts develop severe aneurysmal dilatation or atheromatous obstruction.

Synthetic grafts do not degenerate but lose their flexibility with incorporation of fibrous scar tissue around and between the fibers. Leg flexion for long periods, as in squatting or sleeping, often results in thrombosis in a kinked graft. In our patients with synthetic femoral grafts 48 per cent of those originally successful occluded within 3 years (6).

Because of this high failure rate with graft reconstruction, there has been a steady trend back to femoral endarterectomy. This procedure first recorded by dos Santos and introduced in this country by Julian, by Wylie, and by Barker and their associates has not been adopted enthusiastically by vascular surgeons earlier for several reasons. It is a time consuming and meticulous procedure compared to the much simpler grafting operations. It is potentially a more hazardous procedure than a bypass graft, since acute postoperative thrombosis in the segment treated by endarterectomy will obliterate crucial collateral branches with resultant gangrene. The one most encouraging feature of thromboendarterectomy has been the relative lack of late complications and occlusions that have plagued all grafting procedures. Barker and Hart report excellent long term patency in those extremities with initially good results. They describe follow-up examinations of 38 patients 5 or more years after femoral endarterectomy which revealed that only four segments operated upon had become occluded, in only one of which was the occlusion complete. The other 3 patients retained patency of the proximal portion of the segment. There were no amputations. It seems reasonable to assume that a segment of the patient's own artery treated by endarterectomy remains much more flexible and elastic than a homograft or synthetic tube, thus accounting for the superior long term function.

Having become discouraged with synthetic tube bypass grafts below the inguinal ligament, we returned 6 months ago to endarterectomy for all such lesions. In our experience the semiclosed method of endarterectomy with loops as described by Cannon and associates has not been entirely satisfactory. On several occasions, acute thrombosis in the cleared segment has been found to be due to loose shreds of intimal lining left by the loop. Therefore, a standard procedure was adopted of complete open endarterectomy with careful removal of all atheromatous ma-

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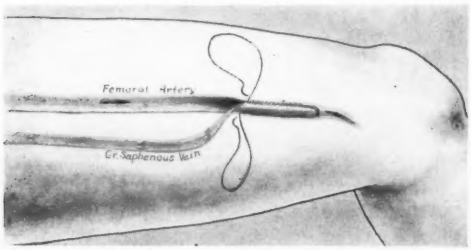

FIG. 1.

FIG. 2.

FIG. 1. Technique of construction of composite saphenous vein-femoral artery tube after endarterectomy.

FIG. 2. Operating table arteriogram of complete femoral artery-vein tube.

terial, followed by closure of the artery over a plastic catheter stent. This technique gave much better results. Distal irrigation with heparin-saline solution through the catheter every 20 minutes, as used by Cannon and his associates, has been very helpful in preventing distal thrombosis.

Occasionally during endarterectomy, despite all these precautions, a very small or contracted segment of reconstructed artery will thrombose acutely a few minutes after restoration of blood flow. The combination of roughened lining and tiny lumen leads to fibrin deposition and occlusion.

It was during such a distressing situation as this, recently, that an impromptu solution to the problem was found which has prompted this report. In order to produce a wider lumen for blood flow through the segment treated by endarterectomy, the patient's saphenous vein was excised, split longitudinally, and inserted as a long patch or roof to the opened artery (Fig. 1). This produced a composite tube, one-half the circumference composed of artery and the other half of vein, with a very adequate lumen. This first patient and 2 subsequent patients with small femoral arteries have had excellent early results from this composite reconstruction. The saphenous vein was selected for the roof rather than a long patch of synthetic material to avoid the kinking tendency of plastic cloth after fibrous incorporation. At the end of each of these procedures an arteriogram was made as a base line to compare with subsequent arteriograms at 6 month intervals (Fig. 2). The chief disadvantage to this procedure is the amount of time required to carry out two long suture lines up each side of the artery-vein junction. It now requires approximately 30 minutes for suturing each side in a common femoral to proximal popliteal reconstruction.

TECHNIQUE

The superficial femoral artery is exposed through a longitudinal incision in the medial thigh, and the sartorius muscle is reflected. The adductor muscle is divided, if necessary, to expose the lower femoral-popliteal junction. All side branches of the artery are temporarily ligated with a No. 00 silk tie using a single knot to prevent back bleeding from collaterals. This technique of control is simpler than using small bull dog clamps which catch sutures. The artery is opened longitudinally over the entire length of obstruction, and thrombus and sclerotic intima are carefully dissected out under direct vision. The lower limit of intimal removal occasionally must be resutured to the vessel wall with interrupted mattress sutures to prevent subintimal dissection of blood. A plastic catheter is inserted into the distal lumen and held in place with an umbilical tape with a rubber tube tourniquet. Every 20 minutes this catheter is irrigated with 10 cubic centimeters of saline solution contain-

ing 10 milligrams of heparin per 100 cubic centimeters. If the remaining arterial wall can be loosely reconstructed over a No. 14 French catheter, no patch is used and the artery is closed with continuous No. 5-0 arterial silk sutures. If a No. 14 French catheter fits tightly or a No. 12 is as large as can be used, the saphenous vein is used to enlarge the lumen. The vein is readily available in the adjacent subcutaneous fat and the proper length is excised, carefully tying all side branches. It is opened longitudinally, the ends are reversed to prevent valve obstruction, and the anastomosis is begun at the distal end. Reversing the vein also joins the larger circumference of proximal vein with the smaller distal artery. It is important to widen the distal lumen at the point of reattachment of distal intima. After suturing with an over-and-over stitch for 1 inch up each side of the artery-vein junction, the vein is stretched to what seems a physiologic degree and attached to the artery with several interrupted sutures near the upper limit of endarterectomy. Now the lower sutures are continued up the two sides to the upper corner, using a No. 18 French plastic catheter as a stent so that the lumen remaining will be uniform and not too large. Before completion of the final upper 1 inch the stent is removed to flush the proximal artery. The anastomosis is completed and the distal clamp is removed. Additional sutures will often be necessary before permanently removing the upper clamp. The temporary sutures are removed from all collateral branches. The adductor tendon is not reconstructed for fear of compressing the artery in Hunter's canal. The wound is closed with interrupted sutures, and no splint is used on the leg. No anticoagulant is used postoperatively.

DISCUSSION

Of 10 consecutive open femoral endarterectomies 3 have required composite reconstruction with saphenous vein. In retrospect, some of the earlier procedures performed without the vein would have resulted in a safer, more generous lumen had this technique been used. All 10 patients, however, have had excellent early results with return of pedal pulses. These patients will be followed up closely with repeat arteriograms. It is believed that this procedure offers the greatest likelihood of long term patency of any we have tried. The disadvantage of reconstruction of the artery with a small lumen after endarterectomy and the shortcomings of a small vein graft alone are both overcome by combining artery and vein. It is believed that this composite tube made entirely with the elastic walls of the patients' own vessels is more likely to remain flexible and patent than when a synthetic tube or homograft is used.

SUMMARY

Femoral-popliteal reconstruction with graft replacement or bypass has resulted in a high rate of late occlusion regardless of the type of graft used. Present evidence suggests that endarterectomy offers the best chance of long term patency. To prevent acute thrombosis which occasionally occurs after endarterectomy of a narrow segment, autogenous saphenous vein has been used to reconstruct a long composite artery-vein tube. This tube of generous dimensions is composed entirely of elastic autogenous vessel wall and should therefore remain much more flexible than homologous artery or synthetic fabric.

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THE SURGEON'S LIBRARY

Reviews of New Books

THE PUBLICATION of *The History of the Royal College of Surgeons of England*[1] is the more welcome because it has been so long needed; without it a knowledge of the development of surgical education would be incomplete.

The lineage of the Royal College covers 500 years, dating from the Company of Barbers and the Guild, through the Company of Surgeons up to the birth of the Royal College of Surgeons in 1800. Up to this time an apprenticeship in surgery, with routine courses, provided the background for the surgeon. William Hunter's Private School of Anatomy and Surgery was notable.

The move of the College from the Old Bailey to the present site was made in 1797 and one of the first meetings of the Court of Examiners was to assess the physical disability of Rear Admiral Sir Horatio Nelson.

On March 22, 1800, the Great Seal was affixed to the charter.

Immediately before this, John Hunter's Museum was transferred to the control of the College. As a result of bombings in World War II about one-half of the specimens were destroyed. Only one-fourth of Hunter's original collection remains.

In its first 50 years, the College survived the trials of adolescence and difficult parental control. Fellowship was instituted in 1843, the new Charter in 1852, and the Medical Act of 1858 followed. Since then, efforts have continued toward unification and simplification of the various professional qualifying examinations and the broadening of the educational background. Appreciation of the intimate relationship of the health sciences, beginning with the Dental Board of 1859, has continued to the present with the recent establishment of the various faculties and departments in the preclinical sciences.

The conservatism of the College was evidenced in various ways. The delayed acceptance of Lister's revolutionary contribution was one of them.

During the two great wars the services of the officials and Fellows of the Royal College were effective and invaluable. The chapter, "Creative Evolution," covering the years 1941 to 1949, and particularly just following the conclusion of World War II, reveals the astounding recuperative power, great vision, and remarkable accomplishment of the College. Under the stimulus afforded by Lord Alfred Webb-Johnson and with his unique fund raising ability, reconstruction plans for the basic sciences and research progressed amazingly and now the Nuffield College of Surgical Sciences, with its great hall, residents' quarters, and research laboratory, is in operation. In 1956, the various benefactors were recognized by the formation of the Court of Patrons.

With its helpful attitude toward the American College of Surgeons and participation in the International Federation of Surgical Colleges, the influence of the Royal College is extending.

This volume is supplemented by excellent chapters on the Library and Museum, by Mr. W. R. Le Fanu and Miss Jessie Dobson, and with excellent illustrations.

The historian, Sir Zachary Cope, combines the abilities of an author, medical writer, and surgeon. In view of his active participation in and familiarity with the workings of the College, his selection could not have been a more appropriate one. The result is an entertaining history desirable for inclusion in every surgical library. —*Howard C. Naffziger.*

THE SECOND EDITION of the excellent textbook *Surgery of Repair as Applied to Hand Injuries*[2] shows no basic change in style or format from the previous edition published 7 years ago. A few additional figures, more detailed information concerning anesthesia, and a clarification of the authors' stand on the indications for primary flexor tendon repair resulted in 27 additional pages.

It is a book specifically aimed at demonstrating what can be accomplished by applying modern principles of plastic surgery and techniques in the treatment of the injured hand. It is in no sense a reference book but, rather, a record of personal experiences. The authors have very carefully delineated the scope of the book in the foreword by saying: "We accept any criticism of incompleteness, believing it better to remain incomplete as a reference book than to transgress beyond the scope of first-hand experience."

[1] THE HISTORY OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND. By Zachary Cope, Kt. 360 pages, illustrated. $13.50. Springfield, Ill.: Charles C Thomas, 1960.

[2] SURGERY OF REPAIR AS APPLIED TO HAND INJURIES. By B. K. Rank, C.M.G., M.S.(Melb.), F.R.C.S.(Eng.), F.R.A.C.S., and A. R. Wakefield, M.S. (Melb.), F.R.C.S.(Eng.), F.R.A.C.S. Foreword by Sir Gordon Gordon-Taylor. 2nd ed. 284 pages, 219 illustrations. $9.00. Baltimore: The Williams & Wilkins Co., 1960.

The chapter on "Examination and Appraisal of a Recently Injured Hand" is well worth the attention of those performing emergency surgery as are the sections devoted to the principles of plastic surgery and to the choice of procedures. In the material regarding anesthesia no mention has been made of the very useful regional block of the median and ulnar nerves as practiced in the United States, and the authors still rely on the Esmarch bandage for a tourniquet in preference to the pneumatic cuff. New illustrations have been added to those on cross finger flaps and the advantages of filleting procedures. The benefits of primary nerve repair are again emphasized. References to Volkmann's contracture are limited to the intrinsic type described by Bunnell.

It is in Chapter 13, "The Secondary Repair of Deep Structures," and in the section on flexor tendons that the authors have clarified the principles of handling isolated profundus tendon injuries and the late reconstruction of the flexor mechanism by free tendon grafts. The more positive statements which were made in the previous edition concerning the importance of the paratenon on the graft have been qualified. Similarly, one notes a more conservative attitude toward the treatment of "mallet finger." The material on the care of that most troublesome "buttonhole" deformity is still rather sketchy.

The authors' discussion on overcoming large defects in nerves is not given in detail, and if this reticence to discuss structures above the wrist is in deference to the restricted title, one can only recall Bunnell's classic definition of the hand as starting mechanically at the elbow and dynamically in the opposite hemisphere!

The question of tendon transfers as a means of providing motions for irreparable nerve lesions is barely touched. A more detailed discussion of these and of some of the useful procedures on the bones and joints would make for a more complete treatment of this phase of secondary repair.

Chapter 17, "Hand Injuries in Children," is excellent, as is the section on burns.

This volume should be a constant source of reference and should be particularly valuable to the industrial surgeon and to the orthopedist. —*Joseph H. Boyes.*

THE AUTHOR'S VIEWS on the pathogenesis and etiology of osteochondritis dissecans and his experience in the treatment of these lesions constitute the monograph entitled *Osteochondritis Dissecans, Loose Bodies in Joints.*[3]

In the first 114 pages, the author has expressed his views regarding the fact that osteochondritis dissecans in childhood may be a sequela of centers of anomalous ossification which may, when superimposed upon these anomalies, produce the classical childhood lesion. In contrast, the same lesion in adults is stated to be due to tangential trauma and frequently is located in the knee, associated with tears of the medial meniscus. In discussing the pathologic changes which occur in these lesions, parallelisms which are mainly unsubstantiated are drawn between osteochondritis dissecans and the osteochondroses of childhood. The first part of the text is well documented with reproductions of roentgenograms. Conclusions on the pathogenesis and subsequent changes are less well documented by histologic evidence. In the latter portion of the book, the author emphasizes the role of conservative surgery in replacing the loose fragments in an effort to preserve joint function. Various techniques and instruments used to accomplish this end are described in detail and, in general, the published results lend authority to his therapeutic principles. This section devoted to treatment is beautifully illustrated with roentgenograms and operative photographs.

—*William F. Enneking.*

THE EPIDEMIC of trauma on the highways continues to grow in severity, and although there is a great deal of literature related to special facets of its medial engineering and legal aspects, the first general survey of the entire problem appears to be *Crash Injuries; the Integrated Medical Aspects of Automobile Injuries and Death,*[4] in which the author has succeeded remarkably well. There are sections on biomechanics; pathomechanics, crash impact, and crash safety engineering; autopsy pathology; hospital morbidity among motorist casualties; delayed complications and residual disabilities; human salvage; and a unified concept of crash injuries. This book does not deal with the diagnosis and treatment of injuries but with the epidemiology of such injuries. Although written by an orthopedist, it does not overemphasize this field. There is, instead, a well balanced consideration of trauma to all areas and systems.

The great value of the book lies in its focus upon the interfaces between medicine, engineering, and the community. Physicians, designers, engineers, law enforcement officers, and legislators will find it of much interest and value. The use of a large number of illustrations of all sorts increases the impact of the contents upon the reader. *Crash Injuries* will be a standard source of information in this field for many years. It is regrettable that its cost may limit the wide distribution it deserves. —*Leonard F. Peltier.*

AT ITS INCEPTION in 1952, the Obstetrics Department of Mount Sinai Hospital established 10 specialty clinics for prenatal problems. As the 49 chapters of the book *Medical, Surgical, and Gynecological Complications of Pregnancy*[5] testifies, through these clinics have come many patients constituting a wealth of associated complications of pregnancy, ranging from such rarely seen diseases in the pregnant woman as sarcoidosis or myasthenia gravis to the everyday problems of salivation and varicose veins.

Each problem or related group of diseases is accorded a separate chapter. There are 68 contributors represented from the staffs in obstetrics and gynecology radiology, ophthalmology, otolaryngology, dermatol-

[3]OSTEOCHONDRITIS DISSECANS, LOOSE BODIES IN JOINTS; ETIOLOGY, PATHOLOGY, TREATMENT. By I. S. Smillie, O.B.E., Ch.M., F.R.C.S.(Ed.), F.R.F.P.S. 224 pages, illustrated. $12.50. Edinburgh and London: E. & S. Livingstone, Ltd., 1960; Baltimore; The Williams & Wilkins Co., exclusive U. S. agents.

[4]CRASH INJURIES; THE INTEGRATED MEDICAL ASPECTS OF AUTOMOBILE INJURIES AND DEATH. By Jacob Kulowski, M.D., F.A.C.S., F.I.C.S. 1080 pages, 531 illustrations. $32.50. Springfield, Ill.: Charles C Thomas, 1960.

[5]MEDICAL, SURGICAL, AND GYNECOLOGICAL COMPLICATIONS OF PREGNANCY. By Alan F. Guttmacher, M.D., and Joseph J. Rovinsky, M.D. 619 pages, 47 illustrations. $16.50. Baltimore: The Williams & Wilkins Co., 1960.

ogy, psychiatry, pathology, and the subspecialties of internal medicine and surgery. Each subject is usually considered from the standpoints of incidence, physiology or pathogenesis, the effect of associated pregnancy, and specific therapy. The treatments outlined are never vague or generalized; drugs, dosages, and times are listed in a definite manner; and therapeutic programs are specifically outlined.

The book contains 619 pages of valuable text with a limited number of illustrations, diagrams, and tables. The careful reader may find an occasional topic or question which has not been covered, but such instances are infrequent. The treatment programs for some of the more common entities might be a subject for discussion, but one can hardly quarrel with the solidly based approach of the individual writer to the problem.

Every chapter maintains a high level of excellence. I particularly enjoyed the chapters on leucorrhea and on radiation, pregnancy and progeny, but everyone will have his own favorites. One can only hope, as new physiology and therapy come to the fore, that this book will appear in revised editions for years to come. It should be available to every doctor who attends the pregnant patient directly or upon referral.

—*Warren H. Pearse.*

A CONCISE DESCRIPTION of the various aspects of transplanting skin homografts obtained at postmortem is contained in the 58 page monograph entitled *Postmortem Homografts*.[6] This method of transplantation is not new, as the authors point out in the first chapter which gives a very brief historical review of the subject. Largely due to the efforts of the authors and their associates in previously published illustrated articles, the use of postmortem skin homografts is becoming increasingly prevalent in surgical centers throughout the country. The title of the book is slightly misleading; its text describes only the preparation and use of postmortem homografts of skin and is not concerned with any other postmortem tissues.

Many of Brown and Fryer's black and white and color photographs amply demonstrate the lifesaving uses of postmortem skin homografts. It is unfortunate, however, that a large proportion of the captions assigned to these photographs are incomplete or confusing, the latter attributable to an amazing lack on the part of the publishers or their proofreaders to detect, prior to publication of this little book, the lapses in English grammar or complete absence of any real conformity between the incomplete captions and the photographs they are supposed to describe. This might detract from the merit of the book, were it not for the foresight and courage of the authors to further inform the general medical public at this time of the importance and merits of employing postmortem skin homografts.

The two most valuable chapters are those dealing with the skin bank storage of postmortem grafts and laboratory investigations of clinical importance. These chapters offer enough detail to permit the average general surgeon to supervise the construction of a skin bank in his local hospital, and the authors have wisely described in the simplest of terms suggestions for the barest necessities required in establishing such a postmortem homograft bank. A brief review of the pertinent literature in these 2 chapters is more accurate than the historical review, and a partial bibliography is supplied at the end of the monograph which should provide the reader with additional information should he wish to more thoroughly investigate this subject.

Both authors should be complimented for their awareness of the special needs for postmortem tissue banks at this time, particularly in view of the possible marked shortage of skin that might exist in these days of threatening atomic or conventional warfare with their catastrophic numbers of burn casualties. I cannot agree with their quick dismissal of the practicability of skin heterografting but unreservedly and enviously wish that I had written in as simple a manner the conclusions so well stated by Brown and Fryer: "It is a dignified surgical procedure . . . removal of the split skin grafts from the person who has died, and covering the wounds of the patient who might otherwise die. Human worth and dignity thus may be carried even beyond death, in that the patient who has just died has saved the life of another patient even after his own death."

—*Blair O. Rogers.*

DURING THE SPAN of the last decade, hematologic knowledge has expanded in prodigious volume. The compilation of this burgeoning wealth of information for purposes of dissemination to students and practitioners of medicine has not been generally satisfactory. The standard textbook of hematology is too encyclopedic, and the sections on hematology in standard texts on medicine are too scanty to meet the needs of the tyro or to subserve the ends of the more knowledgeable but overly busy practitioner. *Fundamentals of Clinical Hematology*[7] is an attempt to tread the middle path, difficult though this may be. It is to the credit of the authors that through most of the journey they have managed to avoid the abyss on the one side and the rocky, infertile plain on the other.

The first chapter is devoted to a succinct rendition of the origin, morphology, function, and chemistry of the blood cells. It is a serviceable chapter devoid of the overuse of the extremely complex, such as one knows to be the case in terms of biochemical kinetics. The second, third, and fourth chapters deal with iron and hemoglobin metabolism and the anemias. This is again a utilitarian section, not overly simplified, containing the essentials of a good diagnostic and therapeutic approach to anemia. Chapter 5 concerns erythrocytosis and erythremia. In the 2 succeeding chapters the problems of hemostasis are discussed. The presentation of coagulation theory is lucid and readily understandable, avoiding semantic and "inter-coagulationist" squabbles. The clinical discussion is quite adequate. Chapter 8 deals with a general resumé of the leucocyte, its variation in disease states, and the problems of neutropenia, agranulocytosis, and infectious mononucleosis. In chapter 9, a review of

[6] POSTMORTEM HOMOGRAFTS. By James Barrett Brown, M.D., F.A.C.S., and Minot P. Fryer, M.D., F.A.C.S. 64 pages, 25 illustrations. $5.50. Springfield, Ill.: Charles C Thomas, 1960.

[7] FUNDAMENTALS OF CLINICAL HEMATOLOGY. By Byrd S. Leavell, M.D., and Oscar A. Thorup, Jr., M.D. 503 pages, 71 illustrations. $10.00. Philadelphia: W. B. Saunders Co., 1960.

the most useful therapeutic agents in the treatment of leukemia and the lymphomas is undertaken, with specific dose recommendations deferred for discussion in chapters 10 and 11 which are devoted to the presentation of these hematologic diseases. Chapter 12 confines itself to a review of hematologic techniques including laboratory procedures. The latter are well chosen, carefully described, and are technically good.

This book subserves its purpose well. There are omissions, such as a lack of discussion of the macroglobulinemic syndromes, paucity of information on the methemoglobinemias, and no allusion to the newer data on hemoglobin transport via haptoglobin complexes. However, these are not serious, and perhaps for the asserted scope of the text rightfully should have been avoided. In some areas there may be disagreement with the authors' implied or stated concepts. The presentations have not been dogmatic, and the approach on the whole has been without undue bias.

The text is documented by both case histories and bibliography. The index is adequate and the reproductions, with few exceptions, are good. The book is strongly recommended to the student and to the physician who wishes to review and be up to date on the subject of hematology. —*Walter A. Rambach.*

THE TEXTBOOK *Allgemeine Pathologie*[8] represents a highly individual approach to the subject influenced by Virchow's *Cellular Pathology*. In organizing the book, Letterer has intentionally used as a starting point, in the broadest sense, the morphologic and physiologic aspects of the cell, instead of the body as a whole with its various pathologic disorders. It is this approach centering upon the phenomena of the living cells as they are pictured in their metabolism, growth, reactivity, motility, and morphology, including the submicroscopic levels, which gives it a specific and personal distinction. Letterer is precise in his exact definitions, apparently because of his thorough training in classical philosophy.

There are two major parts to this book. The first, particularly delightful for the teacher of pathology, clarifies the evolution of pathology as a teaching discipline in relation to the historic and philosophic development of our concepts of disease in general. The second part of the book more or less follows the usual scheme of a textbook of general pathology. The chapter on metabolism which deals predominantly with the so-called degenerative disorders contains an integrated discussion of histochemical and biophysical facts, including a concise outline on the metabolism of heavy metals, water, and gases. The chapter on growth disturbances includes a few instructive schemes on normal growth. The chapter on malformations includes the modern concepts based on Spemann's *organisator* theory and the important results of experimental embryology. The chapter on tumors contains a complete presentation of the newer discoveries of their chemistry and a broad appreciation of the various etiologic factors centering especially on the theory of mutation.

[8]ALLGEMEINE PATHOLOGIE; GRUNDLAGEN UND PROBLEME EIN LEHRBUCH. By Dr. Erich Letterer. 849 pages, 632 illustrations. $16.45. Stuttgart: Georg Thieme, 1959.

The book is written not only for the student and the physician but for the teacher of pathology as well.

It is fitting that a pupil of M. B. Schmidt, the late Professor of Pathology at the University of Würzburg, should give us this magnificently comprehensive work on general pathology. The study of the morphologic disorders of metabolism was a tradition in that institute, which Letterer, also, has carried on at the University of Tübingen. Much of the content of this book, particularly the material in the chapter on disorders of fat and protein metabolism and the chapter on inflammation with the new concept of the "histion" as a tissue unit for reaction to inflammatory stimuli, is based on the original work of Letterer.

Few textbooks on general pathology can claim such complete references to the literature, close to 1,700 in all, generously utilizing American and English publications. Without burdening the text, these references are used as footnotes only; however, there is an alphabetic arrangement of the detailed references appended to each chapter. —*Kornel L. Terplan.*

ANESTHESIA for infants and children requires familiarity with many phases of pediatric surgery, pathology, and physiology, as well as the special anesthetic techniques involved. With this in view, the authors of *Pediatric Anesthesiology*[9] have devoted almost half of their book to background material before directing their discussion toward specific problems of anesthesia. The information is culled from many sources and provides invaluable assistance to the occasional pediatric anesthetist.

The material devoted to anesthetic management outlines the preparation of patients and choice of agent and technique and then describes the anesthetic handling of each type of operation. In general, endotracheal methods are favored using cyclopropane or halothane and semiclosed or nonrebreathing techniques. Special emphasis is justly laid on meticulous supervision and monitoring of patients at all times. The book is carefully prepared and offers easy and interesting reading along with ample illustrations and references. —*Robert M. Smith.*

THE SECOND EDITION of *Body Fluids in Surgery*[10] contains 11 chapters that may be grouped into 4 divisions: (1) normal anatomy and physiology of body water, sodium, potassium, and maintenance of chemical neutrality: (2) basic disturbances of fluid mechanics produced by injury, shock, loss of gastrointestinal secretions, and associated diseases of the heart, liver, and kidneys; (3) diagnosis and treatment of water and salt disequilibria states; and (4) disturbances during infancy and childhood.

The material covering basic disturbances of fluid mechanics produced by injury, shock, loss of gastrointestinal fluids, associated diseases of the heart, liver, and kidneys, together with the author's con-

[9]PEDIATRIC ANESTHESIOLOGY. By M. Digby Leigh, M.D., and M. Kathleen Belton, M.D. 2nd ed. 460 pages, 203 illustrations. $12.00. New York: The Macmillan Co., 1960.

[10]BODY FLUIDS IN SURGERY. By A. W. Wilkinson, Ch.M., F.R.C.S.E., F.R.C.S. 2nd ed. 276 pages, 42 illustrations. $5.00. Edinburgh and London: E. & S. Livingstone Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

cepts of diagnosis and treatment, possess a highly refreshing and candid approach to these problems. In contrast with many similar books, the great emphasis for assaying the need for and type of treatment is directly related to the physical examination of the patient. When integrated with careful interpretation of the history, this method is, undoubtedly, of greater value than the overreliance on plasma chemical data that can be uninformative and often misleading.

This text offers substantial support for those who advocate dextran to be the most efficient plasma substitute. Recommending it principally in the treatment of burns, the author also contends that dextran (6 per cent in 0.9 per cent NaCl—molecular weight, 125,000 to 250,000) is a superior replacement for certain losses of gastrointestinal fluids produced by obstruction or fistula but unaccompanied by a significant inflammatory component as might be contributed by peritonitis.

The chapter on the "Maintenance of Chemical Neutrality," based principally upon the Bronsted-Lowry proposition, is an excellent compendium on this subject and a firm foundation for the understanding of so-called acid-base disturbances for those who should choose to carefully study the material included.

The chapter on "Disturbances During Infancy and Childhood" is worth the price of this book alone and reflects the author's extensive experience in this field. It is recommended for those who perform pediatric surgery.

The book is lucid, easy to read, and a valuable contribution to the literature it represents. If any criticism were to be offered, it would be that the author's vast knowledge of the subject would tend to overwhelm those who might be seeking an introduction or a rapidly applicable practical approach to the clinical problems produced by fluid disequilibrium states in the average surgical patient. —*Robert E. L. Berry.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

The Human Blood Proteins; Methods of Examination and Their Clinical and Practical Significance. Translation from the 3rd rev. ed. by Harvey T. Adelson, M.D. By Prof. Ferdinand Wuhrmann, M.D., and Charlie Wunderly, Ph.D. 491 pages, 179 illustrations. New York and London: Grune & Stratton, Inc., 1960.

Atlas of Exfoliative Cytology—Supplement II. By George N. Papanicolaou, M.D., Ph.D. 80 pages, illustrated. Cambridge, Mass.: Published for the Commonwealth Fund by Harvard University Press, 1960.

Surgery in the Aged. Edited by Frank Glenn, M.D., S. W. Moore, M.D., and John M. Beal, M.D. 534 pages, illustrated. $17.50. New York: McGraw-Hill Book Co., Inc., 1960.

Chemical Osteosynthesis in Orthopaedic Surgery. By Michael P. Mandarino, M.D. 72 pages, 36 illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1960.

Synopsis of Pathology. 5th ed. By W. A. D. Anderson, M.A., M.D., F.A.C.P., F.C.A.P. 875 pages, 418 illustrations. $9.25. St. Louis: The C. V. Mosby Co., 1960.

The Multilingual Manual for Medical Interpreting. By Louis R. M. Del Guercio, M.D. 160 pages. New York: Pacific Printing Co., Inc., 1960.

Family Planning. By J. F. Robinson, M.B., Ch.B. Foreword by Sir Andrew M. Claye, M.D. 65 pages, 15 illustrations. $1.25. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents, 1960.

Adventure to Motherhood. By J. Allan Offen, M.D. 65 pages, illustrated. $2.95. Miami, Fla.: Audio Visual Education Co. of America, Inc., 1960.

Diagnostic Roentgenology of the Digestive Tract Without Contrast Media. By Bernard S. Wolf, M.D., Mansho T. Khilnani, M.B., and Arthur Lautkin, M.D. 180 pages, illustrated. $8.75. New York and London: Grune & Stratton, Inc. 1960.

A Polychrome Atlas of the Brain Stem. By Wendell J. S. Krieg. 20 pages, illustrated. $3.00. Evanston, Ill.: Brain Books, 1960.

Enzymes in Clinical Medicine. By Irving Innerfield, M.D. 334 pages, illustrated. $11.95. New York, Toronto, and London: McGraw-Hill Book Co., Inc., 1960.

The Pharmacology of Anesthetic Drugs. By John Adriani, M.D. 332 pages, illustrated. $11.00. Springfield, Ill.: Charles C Thomas, 1960.

Medical History Making. By Ian Stevenson, M.D. 273 pages, 12 illustrations. $6.50. New York: Paul B. Hoeber, Inc., 1960.

Neoplastic Disease at Various Sites. General Editor: D. W. Smithers, M.D., F.R.C.P., F.F.R. Introductory Volume: A Clinical Prospect of the Cancer Problem. 232 pages, illustrated. $8.50. Edinburgh and London: E. & S. Livingstone Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. Agents.

Rose and Carless Manual of Surgery. Consulting Editor: Sir Cecil Wakeley, Bt., K.B.E., C.B. Editors: Michael Harmer and Selwyn Taylor. 1389 pages, illustrated. $15.00. Baltimore: The Williams & Wilkins Co., 1960.

Diagnostik Kunst und Lehre zu Erkennen. Edited by Prof. Agrege H. Gounelle. Die serologischen Reaktionen bei den parasitaeren und infektioesen Erkrankungen. By M. Faure, R. Pautrizel, and L. Leminor. Foreword by Paul Bordet. 80 pages, illustrated. $1.40. Stuttgart: Georg Thieme Verlag, 1960.

Diagnostik Kunst und Lehre zu Erkennen. Edited by Prof. Agrege H. Gounelle. Die bakteriologischen Untersuchungen und die Resistenzpruefungen gegen Antibiotika. By M. Welsch. 98 pages, illustrated. $1.40. Stuttgart: Georg Thieme Verlag, 1960.

Modern Trends in Diagnostic Radiology. 3rd series. Edited by J. W. McLaren, M.A., M.R.C.P., F.F.R., D.M.R.E. 274 pages, 209 illustrations. $16.00. New York: Paul B. Hoeber, Inc., 1960.

Obstetrics. By J. P. Greenhill. 1052 pages, 903 illustrations. $17.00. Philadelphia; W. B. Saunders Co., 1960.

Sea Within; the Story of Our Body Fluid. By William D. Snively, Jr., M.D. 143 pages, illustrated. $3.95. Philadelphia: J. B. Lippincott Co., 1960.

The Case Reports and Autopsy Reports of Ambroise Paré. Compiled and Edited by Wallace B. Hamby, M.D., F.A.C.S. 191 pages, $6.50. Springfield, Ill.: Charles C Thomas, 1960.